Amsterdam, 24 July 2025
EMADOC-1700519818-2288152
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

Invented name: BAQSIMI

International non-proprietary name: Glucagon

Procedure No. EMA/VR/0000244909

Marketing Authorisation Holder (MAH): Amphastar France Pharmaceuticals

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List of abbreviations

ADA	Antidrug antibodies
AEs	Adverse events
API	Active Pharmaceutical Ingredient
aRMMs	Additional Risk Minimisation Measures
AUC	Area under the curve
BG	Blood Glucose
β-CD	Beta-cyclodextrin
B/R	Benefit/Risk
BW	Body weight
CDS	Core Data Sheet
CL	Clearance
Cmax	Maximum concentration
DPC	Dodecylphosphocholine
EC50	Half-Maximal Effective Concentration
Emax	Maximum Effect
ERA	Environmental Risk Assessment
EU	European Union
F	Bioavailability
IM	Intramuscular
IMG	Intramuscular glucagon
IN	Intranasal
IOV	Inter-Occasion Variability
Ka	Rate of absorption
KIN	Production Rate Constant
KOUT	Elimination Rate Constant
MAA	Marketing Authorisation Application
MDI	Multiple daily doses of Insulin
NG	Nasal glucagon
NIM	Non inferiority margin
PD	Pharmacodynamics
PDCO	Paediatric Committee
PIP	Paediatric Investigation Plan

PK Pharmacokinetics

PL Product Leaflet

RMP Risk Management Plan

SAEs Serious adverse events

SmPC Summary of Product Characteristics

T1D Type 1 diabetes

T2D Type 2 diabetes

TEAEs Treatment-emergent adverse events

US FDA United States Food and Drug Administration

V Volume of distribution

VPC Visual Predictive Check

WHO World Health Organization

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Amphastar France Pharmaceuticals submitted to the European Medicines Agency on 08 January 2025 an application for a variation.

The following changes were proposed:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include treatment of severe hypoglycaemia in paediatric patients aged 1 and over with diabetes mellitus for BAQSIMI, based on final results from study I8R-MC-IGBO. This is an Open-Label, Multi-Center, Single-Dose Study to Assess the Safety, Tolerability, Pharmacodynamics, and Pharmacokinetics of Nasal Glucagon in Paediatric Patients with Type 1 Diabetes Aged 1 to <4 years; As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 1.0 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce a correction in the Package Leaflet.

The variation requested amendments to the Summary of Product Characteristics, Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0301/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0301/2020 was completed.

The Paediatric Committee (PDCO) issued an opinion on compliance for the PIP P/0301/2020.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Karin Janssen van Doorn Co-Rapporteur: Not applicable

Timetable	Actual dates
Submission date	08 Jan 2025
Start of procedure:	26 Jan 2025
CHMP Rapporteur's preliminary assessment report circulated on:	21 March 2025
CHMP Rapporteur's updated assessment report circulated on:	16 Apr 2025
Request for supplementary information adopted by the CHMP on:	25 Apr 2025
MAH's responses submitted to the CHMP on:	22 May 2025
CHMP Rapporteur's preliminary assessment report on the	20 June 2025
CHMP Rapporteur's updated assessment report on the	17 July 2025
PRAC RMP advice and assessment overview adopted by PRAC	10 July 2025
CHMP opinion:	24 July 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Severe hypoglycaemia refers to an episode of clinically significant low glucose levels in blood (<54 mg/dL or <3.0 mmol/L), causing neurological impairment exposing the individual to potential harm and requires the assistance from another person to actively administer carbohydrates, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during a severe event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

Severe hypoglycaemia is one of the most significant complications of diabetes treatment, occurring more frequently in patients with profound endogenous insulin deficiency - type 1 diabetes mellitus (T1D) and advanced type 2 diabetes mellitus (T2D). Episodes of severe hypoglycaemia are characterized by neurological impairment that, if left untreated, can lead to serious consequences, such as loss of consciousness, seizures, coma, adverse cardiovascular outcomes, and even death.

State the claimed therapeutic indication

Baqsimi was so far indicated for the treatment of severe hypoglycaemia in adults, adolescents, and children aged 4 years and over with diabetes mellitus.

Within the current procedure the applicant claimed the following indication:

Baqsimi is indicated for the treatment of severe hypoglycaemia in adults, adolescents, and children aged 1 year and over with diabetes mellitus.

Epidemiology

Hypoglycaemia occurs more frequently in patients with T1D than in patients with T2D treated with insulin, possibly 2 to 3 times more frequently, and the incidence increases with age, disease duration for patients with T1D, and insulin therapy duration for patients with T2D. However, because T2D is more prevalent than T1D, most episodes of hypoglycaemia (including severe) occur in people with T2D. The severity of hypoglycaemia is classified according to the patient's ability to self-treat. For mild hypoglycaemic episodes, symptoms are self-recognized and self-treated.

Severe hypoglycaemia affects approximately 30% (range, 22% to 46%) of patients with T1D annually, at a frequency of 30 to 320 events per 100 patient-years. In insulin-treated patients with T2D, severe hypoglycaemia affects 7% to 25% at a frequency of 10 to 80 events per 100 patient-years.

The incidence of severe hypoglycaemia in children with type 1 diabetes ranges from 1.21 to 30 events per 100 person-years. The prevalence of severe hypoglycaemia in children with type 1 diabetes in the EU also varies, but studies indicate a range of 5 to 20 events per 100 patient-years. This variation is due to differences in healthcare systems, diabetes management practices, and patient populations across different countries.

In a cohort of children and adolescents in Germany and Australia, an incidence of 3.6 events of severe hypoglycaemia and coma per 100 patient-years in 2012 was estimated. Older age was associated with moderately decreased risk of severe hypoglycaemia (6% risk reduction per 1-y age increase) and hypoglycaemic coma (3% risk reduction per 1-y age increase).

Management

Injectable glucagon is a safe and efficacious emergency treatment for severe hypoglycaemia (Glucagon for Injection Product Monograph, 2012; GlucaGen HypoKit United Kingdom Summary of Product Characteristics [UK SmPC], 2015; GlucaGen HypoKit United States Package Insert [USPI], 2015; GlucaGen HypoKit Product Monograph, 2016; Glucagon for Injection USPI, 2017). However, practical considerations, such as the multistep preparation of the solution for administration and injection by untrained users, have limited the use of injectable glucagon and can lead to delays in treatment and increased use of costly emergency medical services.

Peptide hormones are typically administered via a parenteral route such as intravenous, intramuscular, or subcutaneous. Oral administration is not practical since they undergo digestion and inactivation in the gastrointestinal tract and significant first pass metabolism, resulting in significant loss of efficacy. To overcome the usability challenges of injectable therapy and preserve efficacy, intranasal administration of peptide hormones has been studied. Known examples of intranasal peptides include desmopressin, oxytocin, and calcitonin. Nasal delivery of glucagon has previously been shown to increase blood glucose concentration in healthy subjects and patients with T1D.

The present application describes the clinical development of nasal glucagon (NG) and supports the use of NG as a significant improvement in the delivery of treatment for the serious condition of severe hypoglycaemia.

2.1.2. About the product

Nasal glucagon (NG; Baqsimi, code name LY900018; formerly known as AMG504-1 [originally developed by A.M.G Medical Inc. and later by Locemia Solutions ULC]) is a drug/device combination product containing a novel, nasally administered glucagon powder intended for the treatment of severe hypoglycaemia in adult and paediatric patients with diabetes. A 3 mg dose of ready-to-use NG dry powder, which does not require reconstitution, is administered by inserting the tip of the single-use device into the patient's nostril and depressing the plunger to expel the glucagon powder into the nostril where it is passively absorbed in the anterior nasal mucosa. Patients do not need to inhale or breathe deeply after dosing, enabling drug delivery even in unconscious patients.

Glucagon increases blood glucose concentration by activating hepatic glucagon receptors, thereby stimulating glycogen breakdown and release of glucose from the liver. Hepatic stores of glycogen are necessary for glucagon to produce an antihypoglycaemic effect. Glucagon has been used clinically in the treatment of severe hypoglycaemia since the 1950s, and glucagon for injection (produced from animal sources) was first approved by the United States Food and Drug Administration (US FDA) in 1960. Recombinant glucagon was approved for the treatment of severe hypoglycaemia in the 1990s.

The primary sequence of glucagon is highly conserved in mammals and is identical in man, cattle, pigs, dogs, and rats. The synthetic glucagon peptide is structurally identical to naturally occurring human glucagon as well as glucagon extracted from beef and pork pancreas. The drug substance in NG is synthetic glucagon which is the same single-chain, 29 amino acid polypeptide as the recombinant glucagon used in marketed glucagon emergency kits. The NG commercial drug product contains a dry powder formulation, which consists of synthetic glucagon and uses a novel excipient, the phospholipid dodecylphosphocholine (DPC), as a surfactant and absorption enhancer, and beta-cyclodextrin (β-CD) as a filler/bulking agent and absorption enhancer.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

In order to support the extension of indication to paediatric patients 1 to <4 years old, additional evaluations were performed according to a validated PIP P/0301/2020.

2.1.4. General comments on compliance with GCP

The additional study IGBO was conducted in accordance with the protocol and consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines

- applicable ICH GCP Guidelines, and
- applicable laws and regulations.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

The active pharmaceutical ingredient (API) of Baqsimi 3 mg nasal powder, nasal glucagon, is a synthetic peptide structurally identical to naturally occurring glucagon. As a peptide not containing any non-natural amino acids, it belongs to the class of compounds for which ERA studies can be waived.

2.2.2. Discussion on non-clinical aspects

Due to the expansion of the patient population, an increased environmental exposure of the API of Baqsimi 3 mg nasal powder, glucagon, is expected. Glucagon is a peptide structurally identical to the natural occurring pancreatic hormone that increases blood glucose concentration by activating hepatic glucagon receptors.

The synthetic glucagon does not contain any non-natural amino acids and is expected to be degraded in polypeptides that are subject to extensive degradation in sewage treatment. Most importantly, it is a naturally occurring compound. Therefore, the medicinal product Baqsimi 3 mg nasal powder presents no risk to the environment.

There are no other new non-clinical data submitted for this application.

2.2.3. Conclusion on the non-clinical aspects

Considering that Baqsimi (nasal glucagon [NG]) contains a synthetic peptide structurally identical to naturally occurring glucagon. As a peptide not containing any non-natural amino acids, glucagon is not expected to pose a risk to the environment.

No additional new non-clinical data have been submitted in this application, which is considered acceptable.

2.3. Clinical aspects

2.3.1. Introduction

The clinical development program of NG comprises 12 studies that were conducted to evaluate the efficacy, effectiveness, and safety of NG, as well as to characterize NG pharmacokinetics (PK) and pharmacodynamics (PD). At time of initial MAA, the results of 11 completed clinical studies were provided. NG was previously tested in the paediatric population aged between 4 and <17 years in 1 clinical trial (IGBB) and 1 actual-use study (B001). In order to support the extension of indication to paediatric patients 1 to <4 years old, additional evaluations were performed according to a validated PIP:

• Population PK/PD modelling and simulation study to evaluate the use of NG in children 1 to <4 years old

• Data extrapolation to evaluate clinical efficacy in children 1 to <4 years old (see clinical efficacy)

• An additional clinical study to evaluate safety of NG 3 mg in paediatric patients 1 to <4 years old (**Study IGBO**) and confirm PK, PD and efficacy

The PDCO adopted on 18th of October 2024 an opinion confirming the compliance of all studies in the agreed paediatric investigation plan.

During drug development, all studies used clinical trial NG drug product, except adult study IGBI, which used the final commercial NG drug product.

In the newly submitted clinical study IGBO, the same drug-device combination product (i.e. commercial NG drug product) that is approved for use in adults, adolescents, and children aged 4 years and older was used.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 1. Tabular overview of clinical studies

Only study IGBO was newly added as part of this variation application.

Study ID	Population	Design Comparator; Route of Administration	Number of Patients Receiving Study Drug	Key Endpoints
Pivotal Studies				
I8R-MC-IGBC	Adult patients, 18 to 65 years, with T1D or T2D	Multicenter, randomized, open-label, 2-period, crossover; insulin-induced hypoglycemia (insulin infusion was stopped when glucose was <60 mg/dL [3.3 mmol/L]) 1 mg GlucaGen HypoKit; (Novo Nordisk USA); IMG	NG 3 mg: 83 IMG 1 mg: 82 Enrolled/Completed: 83/82	Proportion of patients achieving treatment success, defined as either an increase in glucose to ≥70 mg/dL (3.9 mmol/L), or an increase of ≥20 mg/dL (1.1 mmol/L) from glucose nadir, within 30 minutes after receiving study glucagon, without receiving additional actions to increase glucose level[a]. Safety, PK, and PD
I8R-MC-IGBB	Pediatric patients, 4 to <17 years of age, with T1D	Multicenter, randomized, 2-period, crossover; insulin was used if necessary to attain a glucose <80 mg/dL (4.44 mmol/L) 0.5 or 1 mg GlucaGen HypoKit (Novo Nordisk USA); IMG	NG 2 mg: 23 NG 3 mg: 36 IMG 0.5/1 mg: 24 Enrolled/Completed: 48/47	Proportion of patients achieving treatment success, defined as an increase in glucose of ≥20 mg/dL (1.1 mmol/L) from glucose nadir within 30 minutes after receiving study glucagon, without receiving additional actions to increase glucose level[a,b]. Safety, PK, and PD
Clinical Bridging and Confirmatory Study				
I8R-MC-IGBI	Adult patients, 18 to 64 years, with T1D	Multicenter, randomized, open-label, 2-period, crossover; insulin-induced hypoglycemia (insulin infusion was stopped when glucose was <60 mg/dL [3.3 mmol/L]) 1 mg GlucaGen HypoKit (Novo Nordisk UK); IMG	NG 3 mg: 70 IMG 1 mg: 69 Enrolled/Completed: 70/69	Proportion of patients achieving treatment success, defined as either an increase in glucose to ≥70 mg/dL (3.9 mmol/L), or an increase of ≥20 mg/dL (1.1 mmol/L) from glucose nadir, within 30 minutes after receiving study glucagon, without receiving additional actions to increase glucose level[a]. Safety, PK, and PD

Study ID	Population	Design Comparator; Route of Administration	Number of Patients Receiving Study Drug	Key Endpoints
Supportive Studies				
I8R-MC-IGBD	Healthy adult subjects, 18 to 55 years	Single-center, randomized, open-label,4-period, crossover 1 mg Glucagon for Injection (rDNA origin) (Eli Lilly Canada Inc); SCG	NG 0.5 mg: 15 NG 1 mg: 14 NG 2 mg: 16 SCG 1 mg: 15 Enrolled/Completed: 16/13	Safety, PK, and PD
I8R-MC-IGBA	Adult patients, 18 to 55 years, with T1D	Single-center, randomized, open-label, 3-period, crossover; insulin-induced hypoglycemia 1 mg Glucagon for Injection (rDNA origin) (Eli Lilly Canada Inc.); SCG	NG 1 mg: 12 NG 2 mg: 18 NG 3 mg: 8 SCG 1 mg: 18 Enrolled/Completed: 18/18	Efficacy, safety, PK, and PD
I8R-MC-IGBE	Adult subjects, 18 to 50 years, healthy other than experiencing symptomatic manifestation of the common cold	Single-center, open-label, 2-period, parallel No comparator Concomitant administration of nasal decongestant (ND; oxymetazoline). NG given on 2 occasions to subjects with and without symptoms of common cold and after a single dose with concomitant administration of ND.	NG 3 mg: 36 NG 3 mg with ND: 18 Enrolled/Completed: 36/35	Safety, PK, and PD
I8R-MC-IGBF	Adult patients, 18 to 70 years, with T1D or T2D	Single-center, randomized, open-label, 3-period, parallel 1 mg GlucaGen HypoKit (Novo Nordisk, Canada); IMG	NG 3 mg: 49 IMG 1 mg: 26 Enrolled/Completed: 75/73	Safety and immunogenicity[c]

Study ID	Population	Design Comparator; Route of Administration	Number of Patients Receiving Study Drug	Key Endpoints
I8R-MC-IGBG	Adult patients, 18 to 70 years, with T1D or T2D	Single-center, randomized, open-label, 4-period, crossover. Single 3-mg dose versus repeated 3-mg doses of NG given on 4 occasions. No comparator	NG 3 mg (single dose): 27 NG 6 mg (repeated 3 mg dose): 32 Enrolled/Completed: 32/25	Safety, PK, PD, and immunogenicity[c]
I8R-MC-IGBH[d]	Adult patients, 18 to 70 years, with T1D or T2D	Single-center, randomized, open-label, 4-period, crossover. Single 3-mg dose versus repeated 3-mg doses of NG. No comparator	NG 3 mg (single dose): 3 NG 6 mg (repeated 3 mg dose): 9 Enrolled/Completed: 12/0	Safety, PK, and PD
I8R-MC-IGBO	Pediatric patients, aged 1 to <4 years of age, with T1D	Open-label, multicenter, single-dose study No comparator	NG 3 mg (single dose): 7 Enrolled/Completed: 7/7	Safety, PK, and PD
Actual-Use Studies				
I8R-MC-B002	Adult patients, 18 to 75 years, with T1D	Multicenter, single-arm, open-label No comparator	NG 3 mg: 87 Enrolled/Completed[e]: 129/101	Proportion of patients awakened or returned to normal status within 30 minutes after receiving study glucagon Safety and Immunogenicity[c]
I8R-MC-B001	Pediatric patients, aged 4 to <18 years of age, with T1D	Multicenter, single-arm, open-label No comparator	NG 3 mg: 22 Enrolled/Completed: 26/12	Proportion of patients awakened or returned to normal status within 30 minutes after receiving study glucagon Safety

Abbreviations: IMG = intramuscular glucagon; ND = nasal decongestant; NG = nasal glucagon; PD = pharmacodynamics; PK = pharmacokinetics;
rDNA = recombinant deoxyribonucleic acid; SCG = subcutaneous glucagon; TID = type 1 diabetes mellitus; T2D = type 2 diabetes mellitus; UK = United Kingdom; USA = United States of America.

a Nadir defined as the minimum glucose value at the time of or within 10 minutes following glucagon administration.

b The original efficacy outcome measure in the protocol and statistical analysis plan was "proportion of patients achieving ⩾25 mg/dL (1.4 mmol/L) rise in glucose above basal level". To better facilitate evaluation of the efficacy in pediatric patients, glucose criteria similar to what was used in the adult pivotal study (Study IGBC) were applied retrospectively to Study IGBB.

c Subsequent to study completion, the Sponsor developed a new assay which was used to assess immunogenicity.

d Study IGBH was terminated early due to potential sub-target dosing and was repeated under a new trial alias, Study IGBG. The safety data collected prior to termination of this study are included in the clinical study report included with this submission. Exposure and reasons for discontinuation are also included in the Clinical Summary of Safety.

e Fourteen patients completed Study B002 without a hypoglycemic event and thus were never treated with NG.

2.3.2. Paediatric study IGBO

Study IGBO was a Phase 1, open-label, multi-center study with a primary objective of assessing the safety and tolerability of a single 3 mg dose of the NG commercial drug product in **paediatric participants aged 1 to <4 years with T1D**. Assessment of the PD and PK of 3 mg NG in this patient population were included as secondary objectives. The study comprised a single cohort of 7 patients, with each participant receiving a single dose of 3 mg NG using the same drug-device combination product that is approved for use in adults, adolescents, and children aged 4 years and older.

Blood samples were taken for glucagon PK measurements at 10-, 30- and 60-min post NG administration.
Blood samples for glucose measurements were collected prior to dosing and at 10, 30, 60, and 90 minutes after dosing.

Bioanalytical methods

Concentrations of glucagon were assayed using reversed-phase high performance liquid chromatography with tandem mass spectrometry detection (LC-MS/MS).The LC-MS/MS method involved extraction of glucagon from human plasma using solid-phase extraction in a 96-well format and desThr7-Glucagon as the internal standard (IS). The concentrations were calculated using peak area ratios, and the linearity of the calibration curve was determined using least squares regression analysis employing a weighted (1/x2) linear regression. Quality control samples across the standard curve range were included in each sample analysis batch.

All samples from study IGBO (n=20) were stored at -80°C and analysed within a timeframe of collection, which is contained within the validated storage period at -80°C. Incurred sample reanalysis was conducted, and the results demonstrated a passing rate of 100%.

Plasma concentrations of glucose blood samples were determined by a study-approved rapid glucose analyser (YSI or equivalent).

Pharmacokinetic data analysis and results

The Pharmacokinetics (PK) of NG were analyzed using a population PK approach via nonlinear mixed-effects modelling.

Results

Mean maximum observed glucagon concentrations of 4790 pg/mL were attained at a median time of 10 minutes following a 3 mg NG dose. Model-predicted glucagon geometric mean AUC was 1560 pg*hr/mL.

Figure 1. Mean (± standard deviation) plasma glucagon concentrations following dosing with 3 mg nasal glucagon in paediatric participants 1 to <4 years old with type 1 diabetes – Study IGBO.

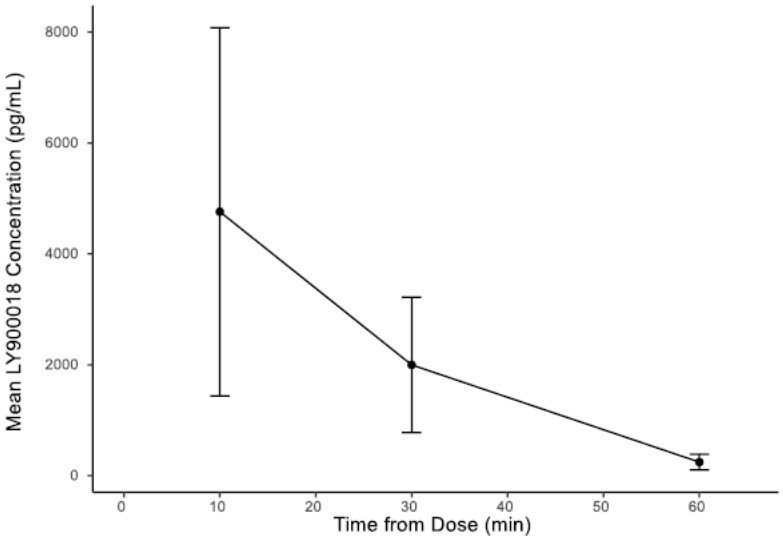

Table 2. Individual and summary statistics of glucagon concentration (pg/ml)

Participant ID	10	30	60
1001	5980	1870	154
2001	1000	1190	456
4001	7170	2980	<100
7001	1030	650	172
7002	3820	623	<100
8001	10200	3270	193
8002	4120	3400	NC
N	7	7	4
Mean	4760	2000	244
SD	3320	1220	142
Median	4120	1870	182.5
Minimum	1000	623	154
Maximum	10200	3400	456
Geometric Mean	3550	1620	220
Geometric CV	115	85	53

Pharmacodynamic results

Following dosing with 3 mg NG, the mean maximum observed BG (BG_{max}) of 242.1 mg/dL (13.4 mmol/L) was achieved at a mean time of 55.6 minutes post-dose and represented a mean increase of 132.4 mg/dL (7.35 mmol/L) from baseline. In individual participants, the change from baseline at the time of BG_{max} ranged from 78 mg/dL (4.33 mmol/L) to 218 mg/dL (12.1 mmol/L).

Table 3. Summary of Blood Glucose Parameters Following Dosing with 3 mg Nasal Glucagon in Paediatric Participants with Type 1 Diabetes.

Summary of the Plasma Glucose Parameters for Study I8R-MC-IGBO

Population: Pharmacodynamic

Parameter	Arithmetic mean (SD) [n] 3 mg nasal glucagon (N=7)
AUC(0-90min) Glucose (mmol.m/L)	1010 (166) [7]
AUC(0-90min) Glucose (mg.m/dL)	18200 (3000) [7]
BGmax (mmol/L)	13.4414 (2.5523) [7]
BGmax (mg/dL)	242.1 (46.0) [7]
Change from baseline of BGmax (mmol/L)	7.3511 (2.9079) [7]
Change from baseline of BGmax (mg/dL)	132.4 (52.4) [7]
TBGmax (min)	55.6 (20.9) [7]

Abbreviations: AUC = area under the concentration-time curve; BGmax = maximum observed blood concentration; N = number of participants; n = number of observations; SD = standard deviation; TBGmax = time of maximum observed blood concentration

Status of Program: Production
Program Location: /cvn/projects/prj/ecb/programs/000000214172/dev/tables/t_ipdp.sas
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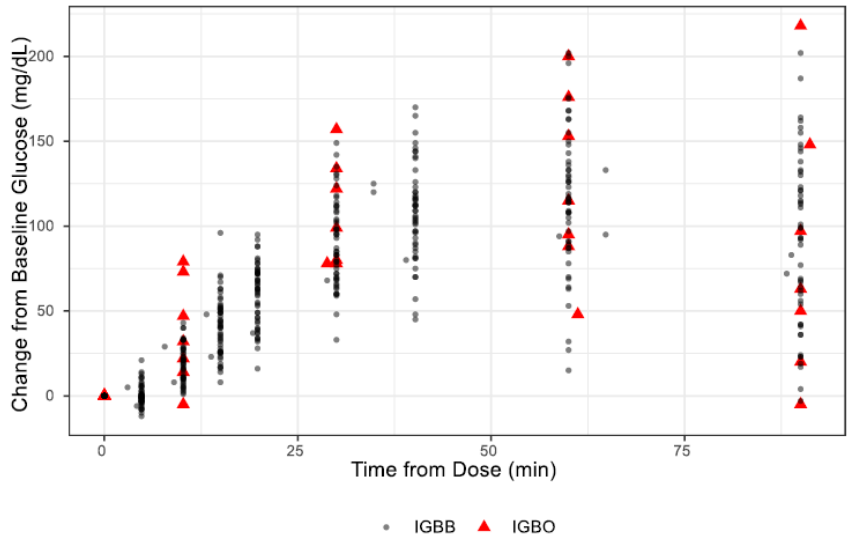
Figure 2. Observed change from baseline glucose concentrations over time in Study IGBO and IGBB.



2.3.3. PK/PD modelling

A **paediatric exposure-response model** was developed (report dated 21 Dec 2018) using data from paediatric patients aged between **4 and <17 years** included in **study IGBB**. The model described the PK and exposure-response relationship of NG (clinical trial drug product) in children aged 4-<17 years and was used to predict the PK exposure and PD response of 3 mg NG (commercial drug product) in children aged 1-<4 years.

Population model building using data from study IGBB

Study IGBB, assessed the PK and PD, efficacy, and safety of NG (clinical trial drug product) in 48 patients (32 males; 16 females). The study included 3 cohorts: 4 to <8, 8 to <12, and 12 to <17 years of age. Either IN (2 or 3 mg) or intramuscular (IM 0.5 mg or 1 mg depending on patient's BW) glucagon was given according to the random assignment. Serial blood samples for PK and PD measurements were drawn.

Population PK and exposure-response analyses of the data from IGBB were performed using NONMEM 7.4. A total of 707 glucagon and 697 glucose concentrations from 48 subjects were included in the NONMEM dataset.

A one-compartment model was used to describe the glucagon concentration data. Standard allometry scaling factors were applied to the Clearance (CL) (power of 0.75) and Volume of Distribution (V) (power of 1). Bioavailability (F) and rate of absorption (Ka) were estimated for NG from Inter-Model Group (IMG). Inter-Occasion Variability (IOV) was also incorporated on Ka and F. A time lag parameter (ALAG) was introduced to better describe the NG absorption. Additionally, baseline glucagon was also estimated in the model. Multiple factors including age and gender were tested for their impact on PK parameters. After applying body weight allometric scaling, age and gender had no impact on glucagon PK.

Table 4. PK parameters in base population model

Parameter Description	Population Estimate (%SEE, 95% CI[a])	Inter-Patient Variability (%SEE[b])
Bioavailability		
F1 for IMG	1 (FIXED)	NE
Rate of Absorption		
Ka (hr^{-1}) of IMG	1.57 (9.62%, 1.33 - 1.89)	NE
Absorption Lag for NG		
ALAG1 (hr)	0.0637 (1.89%, 0.0608 - 0.0670)	NE
Clearance		
CL/F (L/hr)	299 (11.8%, 232 - 365)	53.3% (27.2)
Volume of Distribution		
V/F (L)	28.7 (12.8%, 22.0 - 36.0)	NE
Baseline Glucagon		
BLGCG (pg/mL)	83.8 (9.95%, 69.7 - 100)	75.4% (26.9)
Covariates		
Effect of Nasal administration on F1[c]	-0.784 (3.66%, -0.833 - -0.726)	
Effect of Nasal administration on Ka[d]	0.51 (35.7%, 0.195 - 0.832)	
Inter-occasion Variability on F1	62.2% (27.7, 40.9 - 81.6)	
Inter-occasion Variability on Ka	49% (31.7, 32.8 - 69)	
Residual Error (proportional)[e]	8.1 (13.1%)	

Abbreviations: CL/F = apparent clearance; F1 = bioavailability; IMG = intramuscular glucagon; Ka = absorption rate constant; NE = not estimated; SEE = standard error of the estimate; V/F = apparent volume of distribution.

[a] 95% CI values obtained from bootstrap

[b] Reported as %CV, calculated by the equation $100 \times \sqrt{e^{OMEGA(N)} - 1}$ where OMEGA(N) is the NONMEM output for the inter-subject variability of the N^{th} parameter

[c] $F1 = 1 \times (1 + I1 \times -0.784)$, where I1 is set to 1 when route of administration is nasal and 0 for IMG

[d] $Ka = 1.57 \times (1 + I1 \times 0.51)$, where I1 is set to 1 when route of administration is nasal and 0 for IMG

[e] Reported as %CV, calculated by the equation $100 \times \sqrt{SIGMA}$, where SIGMA is the NONMEM output for the variance of the proportional residual error.

The same model development processes used for PK were adopted for the PD model. An indirect response model was used to describe the glucose response. The final base model included KIN (KIN=E0*KOUT), KOUT, E_{max}, and EC_{50} parameters (KIN: Production Rate Constant; KOUT: Elimination Rate Constant; E_{max}: Maximum Effect; EC_{50}: Half-Maximal Effective Concentration), and a proportional residual error term. Multiple factors including body weight, age, gender, and baseline glucose were tested for their impact on PD parameters and baseline glucose showed an effect on K_{IN}.

Table 5. PD parameters in final model

Parameter Description	Population Estimate (%SEE, 95% CI[a])	Inter-Patient Variability % (%SEE[b])
E0 (mg/dL)	63.1 (16.7%, 43.7 - 88.9)	NE
K_{OUT} (h^{-1})	1.82 (9.29%, 1.47 - 2.25)	23.9% (26.4)
E_{MAX}	3.43 (24.4%, 2.04 - 5.77)	NE
EC_{50} (pg/mL)	413 (26.2%, 252 - 739)	101% (37.8)
Insulin effect on K_{OUT}[d]	0.521 (34.6%, 0.204 - 1.02)	143.7% (39.2)
Half-life of insulin effect (h)	0.097 (16.3%, 0.0706 - 0.155)	NE
Covariate Impact		
Baseline glucose on K_{IN}[c]	0.00218 (45.2%, 0.000820 - 0.0122)	
Residual Error (proportional) [e]	9.7 (15.7%)	

Abbreviations: E0 = estimated baseline glucose in absence of study induced hypoglycemia; EC_{50} = concentration for achieving half of maximum effect; E_{MAX} = maximum effect of glucagon on glucose production rate; K_{IN} = glucose production rate; K_{OUT} = turnover rate of glucose; NE = not estimated; SEE = standard error of the estimate.

[a] 95% CI values obtained from bootstrap

[b] Reported as %CV, calculated by the equation $100 \times \sqrt{e^{OMEGA(N)} - 1}$ where OMEGA(N) is the NONMEM output for the inter-subject variability of the Nth parameter

[c] $K_{IN} = Kout * E0 \times EXP(0.00218 \times (baselineglucose - 72))$, where 72 is the population median baseline glucose in mg/dL

[d] $K_{OUT} = K_{OUT}*(1+0.521)$ while insulin effect is applied.

[e] Reported as %CV, calculated by the equation $100 \times \sqrt{SIGMA}$, where SIGMA is the NONMEM output for the variance of the proportional residual error.

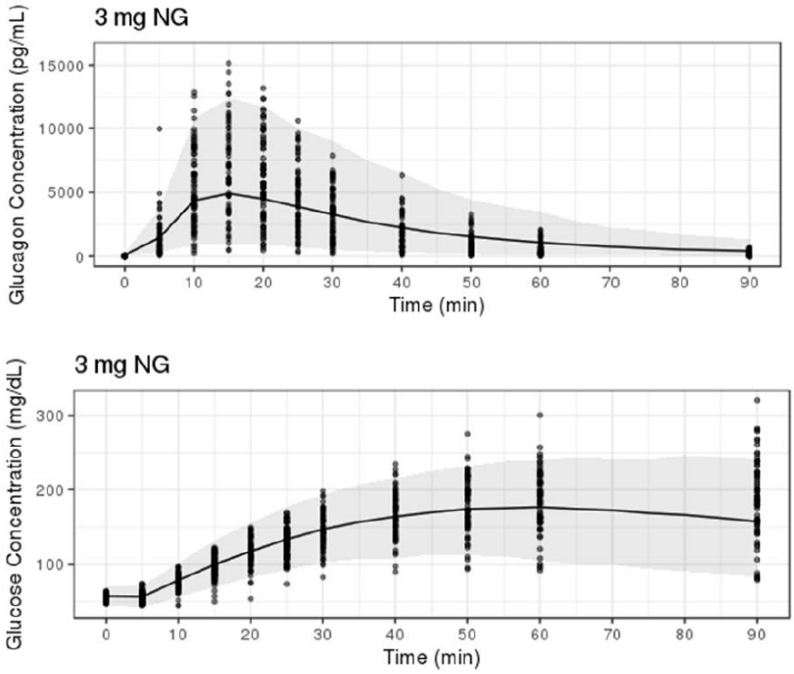
The final PK and PD models were evaluated by bootstrap and by Visual Predictive check (VPC).

Simulation study in children from 1 to less than 4 years of age

To assess the glucagon exposure and glucose response of NG 3 mg with commercially representative drug product in children aged 1 year and older, 2 sets of simulations were conducted:

1. Qualification of paediatric exposure-response model with commercially representative drug product. The commercial NG drug product was introduced in adult study IGBI, whereas all other adult studies and paediatric study IGBB were completed earlier using the clinical trial drug product. In a popPK analysis using pooled data from adult (Studies IGBA, IGBC, IGBD, IGBG, and IGBI) and paediatric patients (IGBB), the exposure difference between adult studies IGBI and IGBC was attributed to a 30% faster rate of absorption (Ka) and 12% higher bioavailability (F) for the commercially representative drug product. Hence, the paediatric IGBB PK model was first updated by increasing the estimated Ka and F values by 30% and 12% respectively for commercially representative drug product, and then the adult glucagon exposure and glucose response were simulated and compared to the observed data in IGBI. The model-predicted glucagon exposure and glucose response of NG 3 mg and IMG 1 mg overlayed well with observations from Study IGBI, indicating the model has the ability to predict exposure and response of NG and IMG for adults with commercially representative drug product.

Figure 3. Predicted glucagon exposure and glucose response in adults over time of NG 3mg overlaid with observations from study IGBI with commercially representative drug product



Abbreviations: IMG = intramuscular glucagon; min = minutes; NG = nasal glucagon.
Note: Solid line represents median of model predictions; shaded area represents 95% prediction interval; black dots are observations from Study IGBI.

2. Prediction of paediatric glucagon exposure and glucose response with commercially representative drug product using the updated IGBB model. Body weight distributions in age of 1-<4 years and 4-<8 years were based on World Health Organization (WHO) growth reference tables. Body-weight distributions in the 8-<12 years and 12 to <18 years age groups were based on the observed data from Study IGBB.

Table 6. Summary of Predicted PK and PD Parameters after Administration of NG 3 mg with Commercially Representative Drug Product

Age group	Dose / Route	C_{max}[a] (pg/mL)	AUC(0-1.5)[a] (pg.h/mL)	BG_{max}[a] (mg/dL)
1 to <4 years	3 mg / NG	18600 [92.4]	8410 [88.3]	213 [18.9]
	0.5 mg / IMG	5580 [95.2]	3450 [88.3]	202 [22.4]
4 to <8 years	3 mg / NG	13500 [91.7]	6170 [90.1]	204 [20.7]
	0.5 or 1 mg / IMG	4100 [97.3]	2600 [88.7]	193 [24.5]
8 to <12 years	3 mg / NG	7380 [87.5]	3550 [83.8]	192 [23.2]
	1 mg / IMG	4210 [89.4]	2750 [83.4]	198 [23.9]
12 to <18 years	3 mg / NG	5800 [87.8]	2860 [81.9]	187 [23.5]
	1 mg / IMG	3220 [88.1]	2130 [82.5]	186 [25.8]

Abbreviations: AUC(0-1.5) = area under the concentration curve from time 0 to 1.5 hours; BG_{max} = maximum blood glucose concentration; C_{max} = maximum concentration; IMG = intramuscular glucagon; NG = nasal glucagon; PD = pharmacodynamics; PK = pharmacokinetics.

[a] Geometric mean [% coefficient of variation] is presented for C_{max}, BG_{max}, and AUC(0-1.5).

Paediatric model update (using data from study IGBO)

The paediatric NG model has now been updated with data from study IGBO, conducted in 7 paediatric participants aged 1 to <4 years, receiving a single dose of 3 mg NG. PK and PD data from Study IGBO were combined with data from the pivotal paediatric study IGBB (4-<17 years). PopPK and exposure-response analyses of the data from Study IGBB and Study IGBO were performed using NONMEM 7.5. The final paediatric PK and PK/PD models were the reference models and were used to estimate parameters with the additional data from Study IGBO.

A total of 718 glucagon (700 from IGBB and 18 from IGBO) and 724 glucose (689 from IGBB and 35 from IGBO) concentrations from 55 participants were included in the dataset.

PK model

As this modelling was based on the previous final paediatric model, the covariate modelling was limited to age, 1 to < 4 years, on F and Ka of NG. Age was tested as a continuous and categorical, IGBO versus IGBB, covariate on both F and Ka parameters.

Standard allometric scaling factors were applied to CL (power of 0.75) and V (power of 1). Different Ka and F were estimated for NG from IMG. IOV was also incorporated on Ka and F. Age as a continuous covariate was tested for impact on F1 and Ka parameters. After applying body weight allometric scaling, age had no impact on glucagon PK. Age as a categorical, IGBO versus IGBB; 1 to <4-year-olds versus > 4-year-olds, was a significant covariate on F1. Model parameters are given in the table below.

The relative F of NG compared to injectable glucagon is estimated to be 22% in Study IGBB and the relative F of NG in Study IGBO compared to injectable glucagon is estimated to be 8%. The lower bioavailability of NG is potentially related to smaller nasal mucosa surface area in very young children aged 1 to < 4 year.

Table 7. PK parameters in base population model

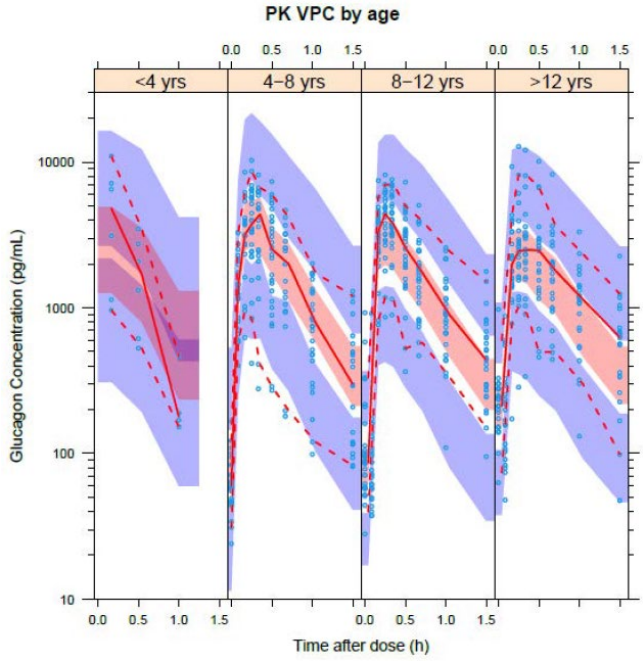
Parameter Description	Population Estimate (%SEE, 95% CI[a])	Inter-Patient Variability (%SEE[b])
Bioavailability		
F1 for IMG	1 (FIXED)	NE
Rate of Absorption		
Ka (hr^{-1}) of IMG	1.64 (9.09%, 1.27 - 1.88)	NE
Absorption Lag for NG		
ALAG1 (hr)	0.0622 (2.75%, 0.0578 - 0.0652)	NE
Clearance		
CL/F (L/hr)	297 (10.0%, 228 - 377)	49.5% (26.5)
Volume of Distribution		
V/F (L)	27.8 (10.9%, 22.8 – 35.7)	NE
Baseline Glucagon		
BLGCG (pg/mL)	82.7 (9.21%, 69.3 - 99.4)	73.8% (27.6)
Covariates		
Effect of Nasal administration on F1 (IGBB)[c]	-0.781 (2.47%, -0.829 - -0.735)	
Effect of Nasal administration on Ka[d]	0.44 (38.4%, 0.216 - 0.952)	
Effect of Study IGBO on F1[f]	-0.616 (17.5%, -0.682 - -0.211)	
Inter-occasion Variability on F1	55.7% (25.4%, 36.5 - 74.3)	
Inter-occasion Variability on Ka	46.3% (23.0%, 35.7 - 59.6)	
Residual Error (proportional)[e]	28.5 (12.9%)	

Abbreviations: ALAG1 = Absorption lag for NG; BLGCG = baseline glucagon; CL/F = apparent clearance; CI = coefficient of variation; CV = coefficient of variation; F1 = bioavailability; IMG = intramuscular glucagon; Ka = absorption rate constant; NE = not estimated; NONMEM = nonlinear mixed effects modeling program; SEE = standard error of the estimate; V/F = apparent volume of distribution.

a 95% CI values obtained from bootstrap.
b Reported as %CV, calculated by the equation 100 × √eOMEGA(N) − 1 where OMEGA(N) is the NONMEM output for the inter-subject variability of the Nth parameter
c F1 = 1 × (1 + ⁄1 × −0.781) , where I1 is set to 1 when route of administration is nasal and 0 for IMG
d Ka = 1.57 × (1 + ⁄1 × 0.51), where I1 is set to 1 when route of administration is nasal and 0 for IMG
e Reported as %CV, calculated by the equation 100 × √SIGMA, where SIGMA is the NONMEM output for the variance of the proportional residual error.
f F1 = 1 × (1 + ⁄1 × −0.781) × (1 + ⁄2 × −0.616), where I1 is set to 1 when route of administration is nasal and 0 for IMG and I2 is set to 1 when study is IGBO and 0 when study is IGBB

The final PK model was evaluated by bootstrap and by VPC. The bootstrap was carried out by sampling from the analysis dataset with replacement, to produce re-sampled datasets with the same number of patients. A total of 500 bootstrap datasets were created.

Figure 4. Visual predictive check for the final pharmacokinetic model (prediction corrected).



PD model

The final model included KIN where KIN=E0*KOUT, KOUT, E_{max}, and EC_{50} parameters, and a proportional residual error term.

Table 8. PD parameters in final model

Parameter Description	Population Estimate (%SEE, 95% CI[a])	Inter-Patient Variability % (%SEE[b])
E0 (mg/dL)	86.2 (34.0%, 57.4 - 135)	NE
K_{OUT} (h^{-1})	2.7 (32.6%, 1.84 - 4.27)	51.7% (54.9)
E_{MAX}	1.99 (69.9%, 0.808 - 3.82)	NE
EC_{50} (pg/mL)	301 (58.5%, 178 - 628)	185% (68.5)
Insulin effect on K_{OUT}	0.895 (63.6%, 0.403 – 1.68)	63.2% (110)
Half-life of insulin effect (h)	0.166 (41.7%, 0.0901 - 0.256)	NE
Covariate Impact		
Baseline glucose on K_{IN}[c]	0.0022 (82.3%, 0.000554 - 0.0111)	
Residual Error (proportional) [d]	10.3 (15.8%)	

Abbreviations: CI = confidence interval; CV = coefficient of variation; E0 = estimated baseline glucose in absence of study induced hypoglycemia; EC_{50} = concentration for achieving half of maximum effect; E_{MAX} = maximum effect of glucagon on glucose production rate; K_{IN} = glucose production rate; K_{OUT} = turnover rate of glucose; NE = not estimated; SEE = standard error of the estimate.

[a] 95% CI values obtained from bootstrap

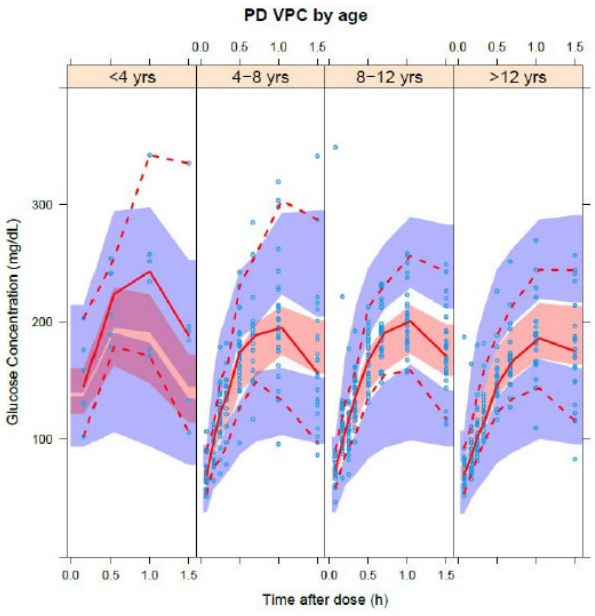
[b] Reported as %CV, calculated by the equation $100 \times \sqrt{e^{OMEGA(N)} - 1}$ where OMEGA(N) is the NONMEM output for the inter-subject variability of the Nth parameter

[c] $K_{IN} = Kout * E0 \times EXP(0.0022 \times (baselineglucose - 72))$, where 72 is the population median baseline glucose in mg/dL

[d] Reported as %CV, calculated by the equation $100 \times \sqrt{SIGMA}$, where SIGMA is the NONMEM output for the variance of the proportional residual error.

The final PD model was evaluated by bootstrap and by VPC.

Figure 5. Visual predictive check for the final glucose exposure-response model (prediction corrected).



2.3.4. Discussion on clinical pharmacology

The PK and PD of NG has previously been investigated in several studies in adults and 1 study in paediatric T1D patients aged 4-<17 years old (study IGBB) as part of the initial marketing authorisation application. With this type II variation, very limited PK and PD data in T1D patients aged 1 to <4 years (n=7) from study IGBO are added. Due to the sparse data, the PK of NG in these young patients were analyzed using a population PK approach based on data from studies IGBB and IGBO.

The model-predicted glucagon geometric mean AUC value of 1560 pg*hr/mL for study IGBO is lower than previously reported AUC values for adults in study IGBI (i.e. 2740 pg*hr/mL) and for paediatric subjects in study IGBB (i.e 2000-2940 pg*hr/mL across paediatric age subcategories). The assumption made by the MAH that the estimated lower bioavailability for study IGBO is potentially related to smaller nasal mucosa surface area in very young children aged 1 to < 4 year is considered plausible, however this remains hypothetical (see risk benefit).

However, the conclusions from a GCP inspection of study IGBB also impacts the reliability of the model-based conclusions for study IGBO. Indeed, a routine GCP inspection of paediatric study IGBB performed in December 2018 and January 2019 identified several critical findings, such as missing instruction on the creation of source data and incorrect handling of PK samples. Therefore, during the initial MAA, only the PD data from study IGBB were considered reliable and were used for MAA. This was considered acceptable, since at doses achieving saturation of the glucose response, glucagon PK data per se are less important and are considered as supportive information. Overall, despite the unreliable PK data, the Benefit/Risk (B/R) of NG in paediatric patients 4 to 17 years old was considered positive based on the PD, efficacy and safety data. Since unreliable PK from study IGBB were now used for building of a paediatric popPK/PD model and given that it is very unlikely that the limited available and usable PK data from study IGBO can be informative for development and adequate validation of a popPK and PK/PD model, no model-based approach can currently be used for analysing PK and PD data in patients aged 1 to <4 years.

With respect to the individual PK data collected in study IGBO, it is noted that similar to previous PK observations with NG, very high variability in glucagon concentrations is observed in this limited dataset. The mean glucagon concentration observed at 10 minutes post-dose across 7 subjects (i.e 4760 pg/ml) is lower than the C_{max} (6130 pg/ml) observed after administration of 3 mg NG (commercial product) to adults in study IGBI. It is however acknowledged that C_{max} cannot be determined precisely for study IGBO based on non-compartmental analysis due to limited sampling (10-, 30- and 60-minutes post-dose), whereas C_{max} was observed at a median time of 15 minutes in study IGBI and IGBB. Based on the data available, the proposed adapted SmPC wording that mean peak levels in patients aged 1 to < 17-year-old is achieved between 10 and 20 minutes is considered acceptable.

Despite the highly variable PK across these 7 paediatric patients, all participants achieved treatment success, defined as achieving ≥20 mg/dL (1.1 mmol/L) increases in plasma glucose within 30 min post-dose. In individual participants, the actual time to treatment success ranged from 10 to 30 minutes, with a mean time to success of 15.6 minutes.

2.3.5. Conclusions on clinical pharmacology

The very limited dataset in patients aged 1 to <4 years old and the lack of a reliable paediatric popPK model hinders firm conclusions on PK in this age group. However, despite large variability in PK, the targeted PD response was achieved (see clinical efficacy discussion).

2.4. Clinical efficacy

Introduction

To address the need for an improved method of glucagon delivery, a clinical development program comprising 12 studies was conducted to evaluate the efficacy, effectiveness, and safety of NG, as well as to characterize NG pharmacokinetics (PK) and pharmacodynamics (PD).

Overall, 461 participants, including adults without diabetes, adults with T1D and T2D, and paediatric patients with T1D, were exposed to NG across the assessed in the initial MAA, 11 completed clinical studies conducted in the US, Canada, and Germany. By its nature as a rescue medication for episodes of severe hypoglycaemia, NG is not intended to be administered regularly.

The goal of glucagon treatment is to increase blood glucose levels rapidly, to the point where the patient with severe hypoglycaemia regains sufficient cognitive function to safely consume oral carbohydrates. The primary goals of the clinical development program were to evaluate glycaemic response of NG compared to injectable glucagon in adult and paediatric patients. To that end, 2 pivotal studies were conducted in controlled clinical settings: an in-patient, insulin-induced hypoglycaemia study in adult patients with T1D or T2D, and an in-patient PK and PD study in paediatric patients (4 to <17 years) with T1D. The efficacy endpoints used in the studies represent a clinically meaningful increase in blood glucose levels to either normalize glycaemia or raise glucose to a level at which cognitive function would be restored such that the patient can safely consume oral carbohydrates.

Baqsimi NG was initially authorized in the EU on 16 December 2019 for severe hypoglycaemia in adults, adolescents, and children aged 4 years and over with diabetes mellitus. The recommended dose is 3 mg glucagon administered into 1 nostril.

2.4.1. Main paediatric studies

Study IGBB

One pivotal study was conducted to compare the response of NG with IMG in a controlled clinical setting in paediatric patients. In addition to the comparison of NG 3 mg to weight-based IMG, the study also included a comparison of NG 2 mg with NG 3 mg as well as a comparison of NG 2 mg to weight-based IMG. This section focuses on the comparison of NG 3 mg and weight-based IMG (0.5 or 1 mg).

Study IGBB was a multicenter, randomized, in-patient, crossover study in 48 patients 4 to <17 years of age with T1D. The study was conducted at sites in the US. Study IGBB was conducted in accordance with the iPSP agreed to by the Applicant and the US FDA and was agreed to by EMA/Paediatric Committee (PDCO) as part of the PIP.

As regulatory agencies agreed that it is not ethical to induce hypoglycaemia in the paediatric population, glucagon was administered in this study after glucose was lowered to <80 mg/dL (4.44 mmol/L) using insulin on the dosing day. Although the primary endpoint was PK and PD, to better facilitate evaluation of the efficacy in paediatric patients, glucose criteria similar to what was used in the adult pivotal study

(Study IGBC) were retrospectively applied to Study IGBB. The proportions of patients achieving a glucose increase of ≥20 mg/dL (1.1 mmol/L) and ≥25 mg/dL (1.4 mmol/L) from nadir within 30 minutes of glucagon administration were used as efficacy outcome measures. Nadir glucose was defined as the minimum glucose measurement at the time of, or within 10 minutes following, glucagon administration. Use of the treatment success threshold of >70 mg/dL (3.9 mmol/L) from Study IGBC was not applicable for Study IGBB because the target glucose was <80 mg/dL (4.44 mmol/L) prior to glucagon administration.

All (100%) patients in both treatment arms across all age groups achieved a glucose increase of ≥20 mg/dL (1.1 mmol/L) and ≥25 mg/dL (1.4 mmol/L) from nadir within 20 minutes of glucagon administration. The mean times to achieve these increases were similar for NG and IMG across all age groups. In both treatment groups across all age groups, glucose levels started to rise quickly.

Across all age groups, NG 3 mg demonstrated a glycaemic response similar to IMG, and glucose levels continued to rise through 60 minutes post glucagon administration (Figure 3).

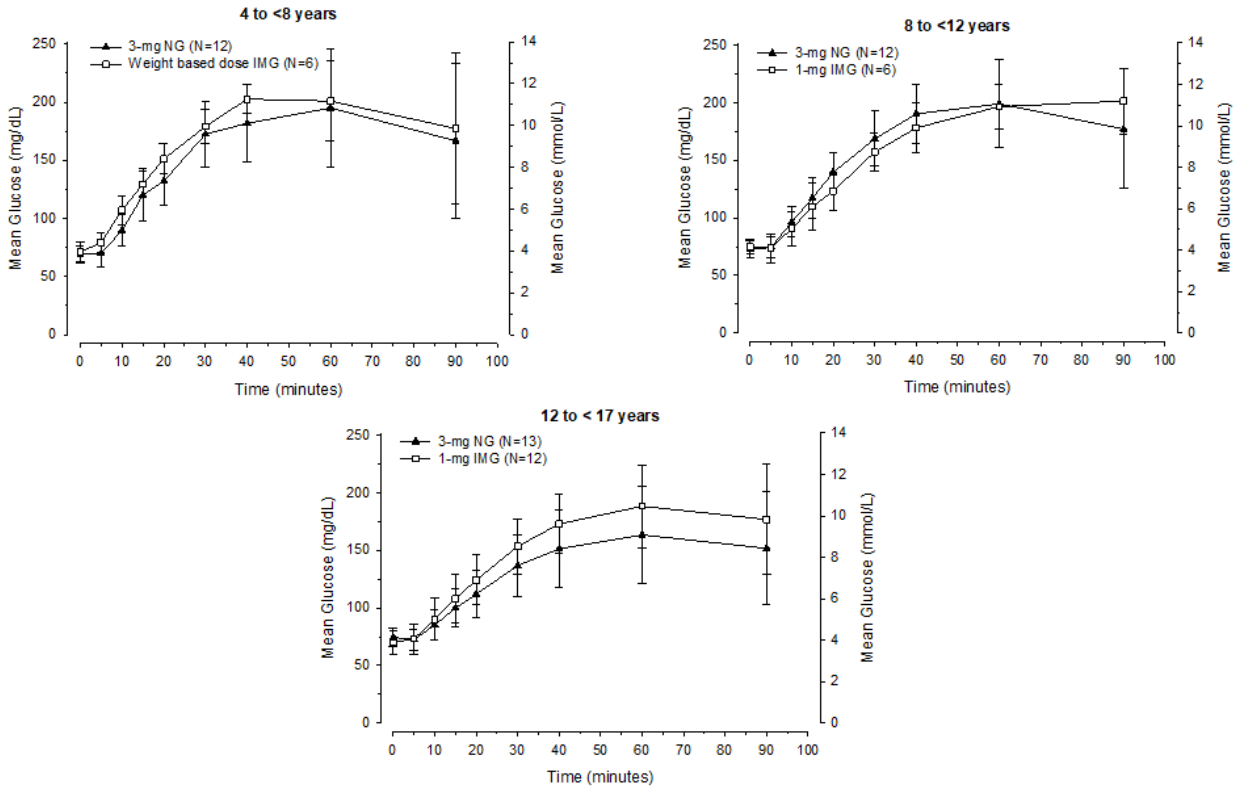
Paediatric exposure-response analysis

Using data from study IGBB, a simulation was performed to estimate glucagon exposures and glucose responses in 1 to <4-year-old paediatric patients; also extended to 4 to <8, 8 to <12 and 12 to <17-year paediatric patients.

The frequency of paediatric patients achieving treatment success based on simulated glucose response data with median baseline glucose of 40mg/dL, by treatment group and by age group was estimated. Treatment success was defined as either an increase in blood glucose to ≥70 mg/dL or an increase of ≥ 20 mg/dL from nadir (defined as minimum glucose value at the time of or within 10 minutes of glucagon administration) within 30 minutes post glucagon dosing.

According to the extrapolation study, a single dose of NG 3 mg would lead to 99.9%-100% of patients achieving treatment success in paediatric patients across all age groups from 1-<18 years old. The median time to achieving treatment success would be 10 minutes in all age groups for paediatric patients treated with NG 3 mg, and more than 97% of patients would achieve treatment success within 15 minutes post NG dosing.

Figure 6 Mean (+/- SD) observed glucose concentration over time by treatment group for the three age groups in Study IGBB.



Abbreviations: IMG = intramuscular glucagon; N = number of patients; NG = nasal glucagon; SD = standard deviation.

Supportive paediatric studies

Paediatric Study IGBO

The supportive Study IGBO was an open-label, multicenter, single-dose study to assess safety, tolerability, and PK and PD properties of NG in paediatric patients 1 to <4 years of age with T1D. The study was conducted at sites in the US, in accordance with the PIP agreed to by EMA Paediatric Committee (PDCO).

Baseline glucose target level

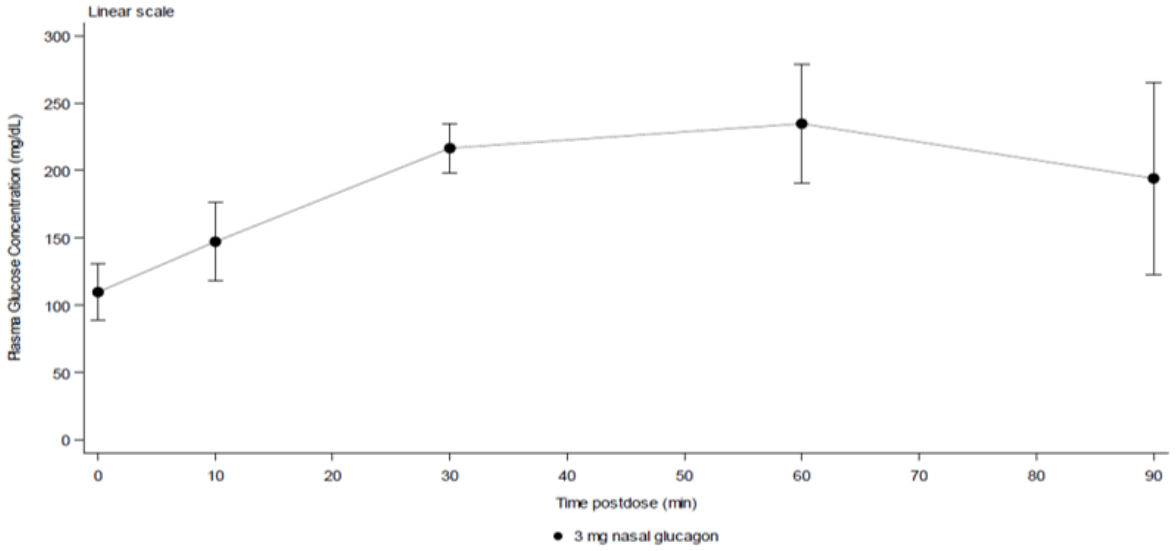
Prior to dosing, each participant's baseline glucose level should be within a target range of 70 to 140 mg/dL for NG to be administered. This range is based on premeal target glucose values recommended by the ISPAD (DiMeglio et al. 2018) of 70 to 130 mg/dL, with a +10 mg/dL allowance for the upper limit.

This study avoids the induction of hypoglycaemia (defined as BG <70 mg/dL; Abraham et al. 2018), to ensure there is no more than a minimal increase in medical risk for the paediatric population.

Although safety and tolerability were the main objectives of the study, efficacy was also assessed based on glucose increases according to the following endpoints: the proportion of patients achieving ≥20 mg/dL (1.1 mmol/L) increases in plasma glucose within 30 min post dose, and the time to reach ≥20 mg/dL (1.1 mmol/L) plasma glucose increases. All participants achieved treatment success within the 30-minutes post dose assessment window. In individual participants, the actual time to treatment success ranged from 10 to 30 minutes, with a mean time to success of 15.6 minutes. Consistently with the older

paediatric age groups, after administration of NG 3 mg dose glucose levels continued to rise through 60 minutes post dose.

Figure 7 Mean (+/- SD) observed glucose concentration over time for the 1 to <4 years old age group in Study IGBO.



Source: Study IGBO, Figure IGBO.5.3.

The primary endpoint was the incidence of TEAEs in paediatric patients with T1D aged 1 to <4 years administered a single dose of NG 3 mg dose (see Clinical Safety below).

Paediatric Actual Use Study B001

Similar to the adult actual-use study (Study B002), a study was conducted to evaluate the real-world effectiveness of NG when administered by the intended users (caregivers) in treating severe or moderate hypoglycaemia in paediatric patients with T1D. Study B001 was a supportive, multicenter, single arm, open-label, actual-use study for which the primary endpoint was the proportion of patients with severe or moderate hypoglycaemia who awakened or returned to a normal status (per caregiver's judgement) within 30 minutes following administration of a single dose of NG 3 mg. Severe hypoglycaemia was defined as an episode associated with severe neuroglycopenia that usually resulted in coma or seizure and required parenteral therapy (glucagon or intravenous glucose). Moderate hypoglycaemia was defined as an episode wherein the child/adolescent with diabetes had symptoms and/or signs of neuroglycopenia and had a blood glucose of ≤70 mg/dL (3.9 mmol/L) based on a blood sample taken at or near the time of treatment. Patients who had a history of severe episodes of hypoglycaemia were not excluded from the study. These patients and their caregivers were asked to use NG 3 mg as necessary for up to 6 months to treat incident episodes of severe or moderate hypoglycaemia.

No severe hypoglycaemic events per protocol definition were reported. This may be explained by the fact that symptoms of hypoglycaemia and physiological hormone responses may occur at a higher glucose level in children compared to adults and that most caregivers usually intervene early, at the first sign of hypoglycaemia before severe hypoglycaemia sets in. All moderate hypoglycaemic events (n=33, 100%) from all 14 patients (100%) in the efficacy analysis met the primary endpoint, defined as patients awakened or returned to normal status within 30 minutes after NG administration.

Although there were no severe hypoglycaemic events in this study, clinically significant hypoglycaemia or major hypoglycaemia, defined as a blood glucose level of <54 mg/dL (3.0 mmol/L), were reported. Importantly, all clinically significant hypoglycaemic events (n = 17) were resolved within 30 minutes.

In this study, no caregivers called for external professional emergency medical assistance. No patients ingested oral carbohydrates or used an injectable glucagon kit before the hypoglycaemic event was resolved. In addition, for most of the hypoglycaemic events (93.9%), caregivers reported that it was easy or very easy to administer NG and that they were relatively satisfied, satisfied, or very satisfied with the use of NG.

Extrapolation Study to Evaluate Clinical Efficacy of Intranasal Glucagon (AMG504-1) in Children from 1 to Less than 4 Years of Age with Hypoglycaemia (PIP Study 7)

This section addresses the EMA PIP requirement for Study 7, based on the simulated glucose response data from Study 6 of paediatric patients aged 1-<4, 4-<12 and 12-<18 years.

Table 9 summarizes the frequency of paediatric patients achieving treatment success based on simulated glucose response data with median baseline glucose of 40mg/dL, by treatment group and by age group (1-<4, 4-<12, and 12-<18 years old). Treatment success is defined as either an increase in blood glucose to ≥70 mg/dL or an increase of ≥20 mg/dL from nadir (defined as minimum glucose value at the time of or within 10 minutes of glucagon administration) within 30 minutes post glucagon dosing.

Figure 8, Figure 9 and Figure 10 show the Kaplan-Meier estimator of the time to achieving treatment success based on simulated data by treatment groups for 1-<4, 4-<12, and 12-<18 year-old age groups, respectively.

The analysis results show that a single dose of NG 3 mg would lead to 99.9%-100% of patients achieving treatment success in paediatric patients across all 3 age groups from 1-<18 years old. The Kaplan-Meier analysis showed that the median time to achieving treatment success would be 10 minutes in all 3 age groups for paediatric patients treated with NG 3 mg, and more than 97% of patients would achieve treatment success within 15 minutes post NG dosing in all 3 age groups (Figure 8, Figure 9 and Figure 8).

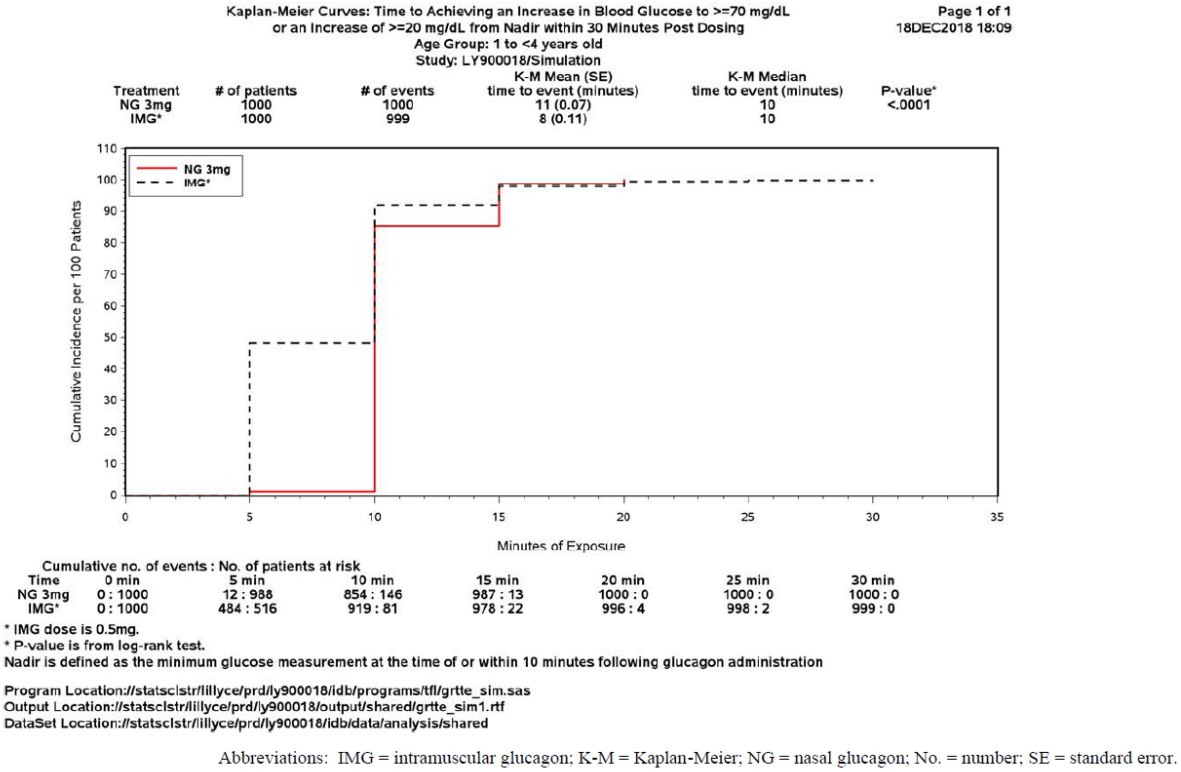
Table 1 Proportion of Patients Achieving Treatment Success

Age Group	Treatment	Treatment Success n(%)
1-<4 years old	NG 3 mg (N=1000)	1000(100.00)
	IMG* (N=1000)	999(99.90)
4-<12 years old	NG 3 mg (N=2000)	1999(99.95)
	IMG* (N=2000)	1999(99.95)
12-<18 years old	NG 3 mg (N=1000)	1000(100.00)
	IMG* (N=1000)	999(99.90)

Abbreviations: IMG = intramuscular glucagon; n = number; NG = nasal glucagon.
* for 1-<4, IMG dose is 0.5 mg; for 12-<18, IMG dose is 1 mg;

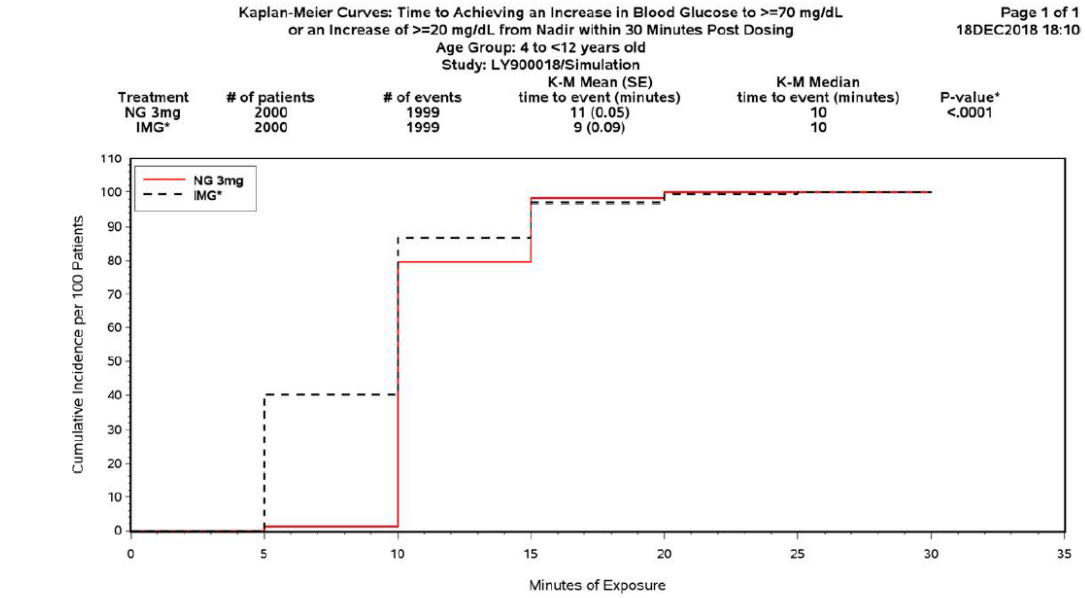
for 4-<12, IMG dose is 0.5 mg for patients with body weight <25 kg and 1 mg otherwise.
Treatment success is defined as achieved an increase in glucose to >=70 mg/dL or an increase of >=20 mg/dl from Nadir within 30 minutes post glucagon administration.
Nadir is defined as the minimum glucose measurement at the time of or within 10 minutes following glucagon administration
Program: lillyce/prd/ly900018/idb/programs/tfl/smtte_sim.sas
Output: lillyce/prd/ly900018/idb/output/shared/smtte_sim.rtf
Dataset: lillyce/prd/ly900018/idb/data/analysis/shared/sim_results.csv

Figure 8 Kaplan-Meier curve of time to achieving treatment success (1-<4 years)



Abbreviations: IMG = intramuscular glucagon; K-M = Kaplan-Meier; NG = nasal glucagon; No. = number; SE = standard error.

Figure 9 Kaplan-Meier Curve of time to achieving treatment success (4-<12 years).



Cumulative no. of events : No. of patients at risk

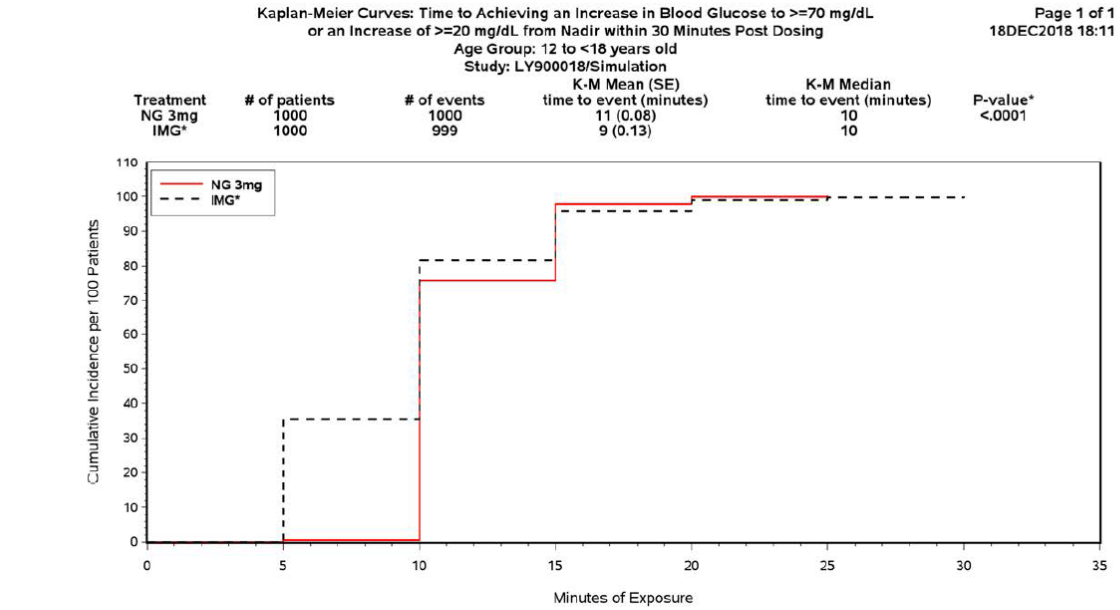
Time	0 min	5 min	10 min	15 min	20 min	25 min	30 min
NG 3mg	0 : 2000	25 : 1975	1594 : 406	1965 : 35	1998 : 2	1998 : 2	1999 : 0
IMG*	0 : 2000	806 : 1194	1734 : 266	1938 : 62	1988 : 12	1998 : 2	1999 : 0

* IMG dose is 0.5 mg for patients weighted <25 kg and 1 mg otherwise.
* P-value is from log-rank test.
Nadir is defined as the minimum glucose measurement at the time of or within 10 minutes following glucagon administration

Program Location://statsclstr/lillyce/prd/ly900018/idb/programs/tfl/grtte_sim.sas
Output Location://statsclstr/lillyce/prd/ly900018/output/shared/grtte_sim2.rtf
DataSet Location://statsclstr/lillyce/prd/ly900018/idb/data/analysis/shared

Abbreviations: IMG = intramuscular glucagon; K-M = Kaplan-Meier; NG = nasal glucagon; No. = number; SE = standard error.

Figure 10 Kaplan-Meier curve of time to achieving treatment success (12-<18 years).



Cumulative no. of events : No. of patients at risk

Time	0 min	5 min	10 min	15 min	20 min	25 min	30 min
NG 3mg	0 : 1000	4 : 996	757 : 243	980 : 20	999 : 1	1000 : 0	1000 : 0
IMG*	0 : 1000	355 : 645	816 : 184	958 : 42	990 : 10	997 : 3	999 : 0

* IMG dose is 1mg.
* P-value is from log-rank test.
Nadir is defined as the minimum glucose measurement at the time of or within 10 minutes following glucagon administration

Program Location://statsclstr/lillyce/prd/ly900018/idb/programs/tfl/grtte_sim.sas
Output Location://statsclstr/lillyce/prd/ly900018/output/shared/grtte_sim3.rtf
DataSet Location://statsclstr/lillyce/prd/ly900018/idb/data/analysis/shared

Abbreviations: IMG = intramuscular glucagon; K-M = Kaplan-Meier; NG = nasal glucagon; No. = number; SE = standard error.

Adult Pivotal Study IGBC

One pivotal study was conducted to compare the response of NG 3 mg with IMG 1 mg in a controlled clinical setting in adult patients. Study IGBC was a randomized, multicenter, open-label, in-patient, insulin-induced hypoglycaemia study in 83 patients 18 to 65 years of age with T1D or T2D. The study was conducted at sites in the US. The patient population was predominantly white; the majority were diagnosed with T1D.

Patients underwent two (2) dosing visits (1 to 4 weeks apart) and were randomized to receive either NG 3 mg or IMG 1 mg at their first dosing visit and received the other glucagon preparation in a crossover fashion at their second dosing visit. Insulin was used to reduce blood glucose levels to the hypoglycaemic range while ensuring patients did not lose consciousness. While loss of consciousness or convulsions may occur in patients with severe hypoglycaemia, current ethics review boards are unlikely to approve, and few patients are likely to enrol in, a study that induces hypoglycaemia that is so severe that consciousness is lost. The study design targeted a blood glucose nadir of <50 mg/dL (2.8 mmol/L), a level of hypoglycaemia low enough to generate clinical symptoms and onset of cognitive impairment but with less risk of loss of consciousness. The insulin infusion was stopped when the blood glucose reached <60 mg/dL (3.3 mmol/L), and study drug was administered approximately 5 minutes after. Due to the residual activity of circulating insulin after stopping the insulin infusion, nadir glucose was defined as the minimum glucose measurement at the time of, or within 10 minutes following, glucagon administration.

The primary efficacy outcome measure was the proportion of patients achieving treatment success, which was defined as either an increase in blood glucose to ≥70 mg/dL (3.9 mmol/L) or an increase of ≥20 mg/dL (1.1 mmol/L) from glucose nadir within 30 minutes after receiving study glucagon without receiving additional actions to increase the blood glucose level. This success criterion accounts for the treatment goal to either normalize glycaemia or raise glucose to a level at which cognitive function would allow further treatment with oral carbohydrates. Health Canada (05 November 2012) and the MHRA (22 November 2012) endorsed the use of the ≥70 mg/dL (3.9 mmol/L) threshold to define treatment success for Study IGBC; the outcome of a blood glucose increase of ≥20 mg/dL (1.1 mmol/L) was added to the protocol during consultation with US FDA. Both definitions of treatment success and the primary efficacy endpoint were agreed to by the US FDA under the SPA for Study IGBC (18 November 2013).

A margin of 10% was used in Study IGBC to assess the non-inferiority of NG to IMG. The margin of 10% was chosen, based on the data for glucagon injection in a simulated emergency study where 10% of participants (parents of children and adolescents with T1D) entirely failed to administer the injectable glucagon product (Harris et al. 2001). From a clinical trial perspective, 10% is an acceptable NIM between the 2 treatments because this could be offset by the possibility that 10% of patients in the real-world setting might not receive any injectable glucagon treatment at all due to the complexity to prepare and administer the dose. The NIM of 10% was endorsed by US FDA under the SPA for Study IGBC (18 November 2013).

In the primary analysis population, comprised of patients with T1D with a glucose nadir of <70 mg/dL (3.9 mmol/L) (N=75), the proportions of patients in the NG 3 mg and IMG 1 mg treatment groups who achieved treatment success were 98.7% and 100%, respectively. The difference in the proportion of patients who achieved treatment success was 1.3%, with the 1-sided upper 97.5% confidence interval of 4.0%, which is below the NIM of 10%; thus, NG demonstrated non-inferiority to IMG in reversing insulin-induced hypoglycaemia.

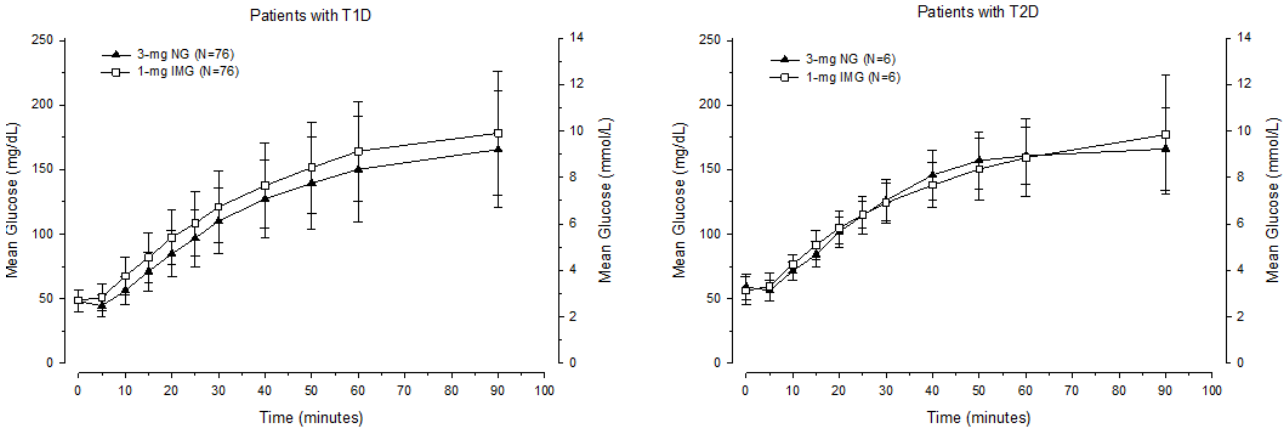
In the primary analysis population, 97.3% of patients in the NG 3 mg treatment group and 98.7% of patients in the IMG 1 mg treatment group achieved both glucose criteria of treatment success. The 1 patient who did not achieve treatment success after administration of NG 3 mg had a nadir glucose concentration of 47 mg/dL (2.6 mmol/L) which increased to 65 mg/dL (3.6 mmol/L) by 30 minutes and

to 72 mg/dL (4.0 mmol/L) by 40 minutes without any other intervention. Of the 5 patients with T2D included in the efficacy analysis, 100% achieved treatment success within 30 minutes of glucagon administration.

Glucose time course data were generated by diabetes type, including all patients who had evaluable glucose values at both dosing visits (Figure 11). In patients with T1D and T2D, NG 3 mg and IMG 1 mg had a similar rate of glucose rise and demonstrated similar magnitude of glucose raising effect through 90 minutes.

Since the goal of insulin infusion in this study was to induce hypoglycaemia to a glucose target of <50 mg/dL (2.8 mmol/L), a prespecified sensitivity analysis was performed to evaluate efficacy in the population of patients with T1D with a glucose nadir of <50 mg/dL (2.8 mmol/L) in both dosing visits (n = 39 [52%]). In this analysis, NG also demonstrated non-inferiority to IMG in the proportion of patients achieving treatment success.

Figure 11 Mean (+/- SD) observed glucose concentration over time after glucagon administration by treatment groups in patients with T1D and T2D in Study IGBC.



Abbreviations: IMG = intramuscular glucagon; N = number of patients; NG = nasal glucagon; T1D = type 1 diabetes mellitus; T2D = type 2 diabetes mellitus: SD = standard deviation.
Note: Figures exclude data after feeding.

The mean time to treatment success in patients with T1D, which is the time from glucagon administration to treatment success and does not include glucagon preparation time, was 16.2 minutes in the NG 3 mg treatment group and 12.2 minutes in the IMG 1 mg treatment group. Similarly, a 3-minute difference between NG and IMG in time to treatment success was observed in the subgroup of patients with T1D who had a glucose nadir of <50 mg/dL (2.8 mmol/L).

To evaluate hypoglycaemic recovery after administration of glucagon, the Edinburgh Hypoglycaemia Symptom Questionnaire was used to collect data on signs and symptoms of hypoglycaemia in Study IGBC (Edinburgh Hypoglycaemia Symptom Questionnaire). Prior to glucagon administration, most patients had mild symptoms which were similar between treatment groups. At 30 minutes post glucagon administration, both treatment groups had similar improvement of symptoms.

Clinical Bridging and Confirmatory Study IGBI and Indirect Comparison with Pivotal Study IGBC

To supplement the analytical comparability program, the adult clinical bridging and confirmatory study, Study IGBI, was conducted to allow an assessment of clinical comparability between the commercial and clinical trial drug products. This approach was agreed upon between the Sponsor and US FDA (Meeting Minutes, 09 December 2016). Study IGBI was a multicenter, randomized, open-label study using the NG commercial drug product, similar in design to Study IGBC, with similar enrolment criteria, same active comparator, and same primary efficacy endpoint. This study was conducted at 2 clinical sites in Germany. The following two-pronged approach using data from Study IGBI was undertaken to link the commercial drug product with the efficacy data from the pivotal study (Study IGBC).

- A within-study comparison was conducted to demonstrate a non-inferior efficacy of NG 3 mg commercial drug product compared to IMG 1 mg in Study IGBI.

- An indirect between-study comparison was conducted to demonstrate a non-inferior efficacy between the commercial NG drug product used in Study IGBI compared to the NG drug product used in Study IGBC.

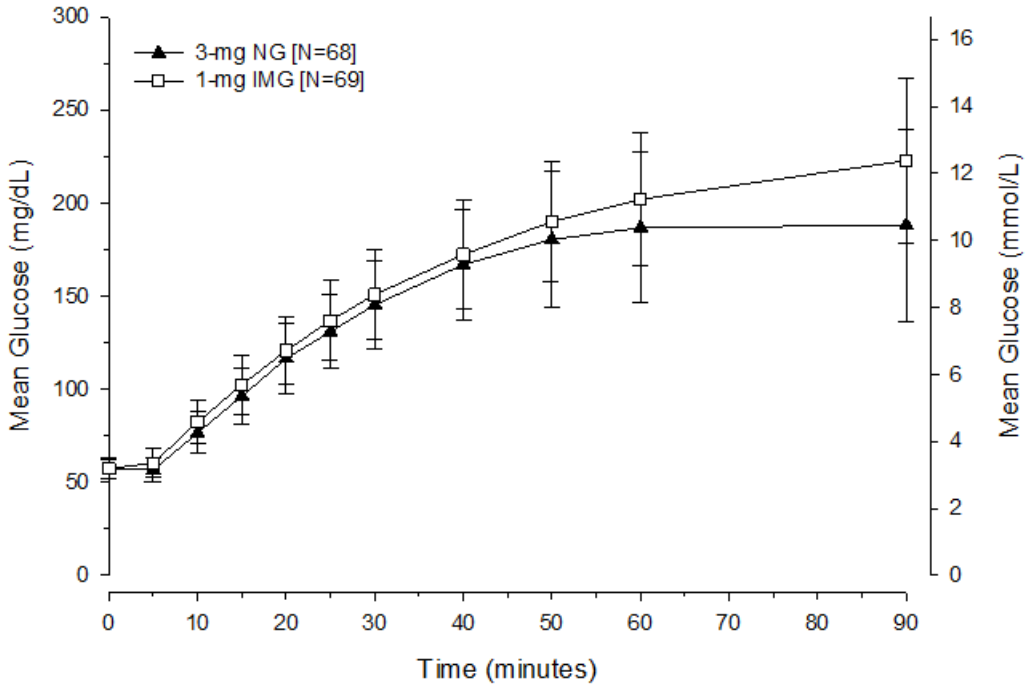
The IMG comparator arm was incorporated to provide a relative comparison with NG 3 mg, thus allowing an indirect comparison. The indirect between-study comparison was performed based on the risk difference observed in Study IGBC (RD1) and the risk difference observed in Study IGBI (RD2). The RD1 and RD2 was calculated as the difference between IMG and NG in the proportion of patients achieving treatment success. If the upper limit of the 2-sided 95% confidence interval of the difference between RD1 and RD2 was below 10%, the commercial drug product was declared to be non-inferior to the clinical trial drug product.

<u>Within-study comparison</u>

The within-study comparison demonstrated non-inferiority in treatment success of NG 3 mg compared to IMG 1 mg in Study IGBI with 100% of patients in both groups achieving treatment success. The mean time to treatment success was 11.4 minutes in the NG 3-mg treatment group and 9.9 minutes in the IMG 1-mg treatment group (Time to Treatment Success). These findings indicate that the efficacy of the NG commercial drug product is comparable with the currently marketed glucagon emergency kit.

Nasal glucagon 3 mg demonstrated a similar glycaemic response to IMG 1 mg through 40 minutes post-glucagon dosing. Afterwards, at the 50-minute time point the glucose profiles began to diverge; whereas the glucose profile with NG began to plateau, the glucose profile with IMG continued to increase (Figure 12).

Figure 12 Mean (+/- SD) observed glucose concentration over time after glucagon administration by treatment groups in patients with T1D in Study IGBI, Full Analysis Set.



Abbreviations: IMG = intramuscular glucagon; N = number of patients; NG = nasal glucagon; SD = standard deviation; T1D = type 1 diabetes mellitus.

Between-study comparison

The indirect between-study comparison demonstrated non-inferiority in the proportion of patients achieving treatment success of the commercial drug product used in Study IGBI compared to the clinical trial drug product used in Study IGBC in patients with T1D (Table 10). These findings demonstrate clinical comparability in that the efficacy seen with the commercial drug product is comparable with the efficacy seen with the clinical trial drug product used in the pivotal study, thus allowing reliance on the efficacy data generated throughout the NG clinical development program.

Table 10. Indirect Comparison of Treatment Success of Nasal Glucagon used in Pivotal Clinical Study IGBC and Clinical Bridging and Confirmatory Study IGBI

	Primary Efficacy Analysis IGBC (T1D) N=75[a]		Primary Efficacy Analysis IGBI (T1D) N=66[a]	
	NG 3 mg	IMG 1 mg	NG 3 mg	IMG 1 mg
Treatment Success – n (%)	74 (98.7%)	75 (100%)	66 (100%)	66 (100%)
Treatment Difference (Confidence Interval)[b]	1.3% (4.0%)[c]		0% (1.5%)[d]	
Indirect Comparison (Confidence Interval)	-1.3% (2.7%)[d,e]			

Abbreviations: CI = confidence interval; CSR = clinical study report; IMG = intramuscular glucagon; n = number of patients in the specified group; N = number of patients in the analysis population; NG = nasal glucagon; NIM = non-inferiority margin; T1D = type 1 diabetes mellitus.

a The Efficacy Analysis Population consisted of all patients who received both doses of the study drug with evaluable primary outcome.

b Difference calculated as (percentage with success in IMG) – (percentage with success in NG); NIM = 10%.

c 1-sided 97.5% CI from a 1-sample mean of the paired differences in occurrence of outcome.

d Upper limit of the 2-sided 95% CI from Wald method with continuity correction.

e Difference calculated as (treatment difference in IGBI) – (treatment difference in IGBC); NIM = 10%.

Sources: Study IGBC CSR, Table 11.4-1; Study IGBI CSR, Table IGBI.7.1; CLUWE////statsclstr/lillyce/prd/ly900018/i8r_mc_igbi/csr1/output/shared/tfl/igbi_smnim11.rtf; CLUWE//statsclstr/lillyce/prd/ly900018/idb/output/shared/smnim11.rtf.

Adult Actual Use Study B002

Study B002 was a supportive, multicenter, single-arm, open-label, actual-use study in adult patients with T1D. The primary endpoint was the proportion of patients with severe or moderate hypoglycaemia awakening or returning to a normal status (per caregiver's judgement) within 30 minutes following administration of NG. This study was conducted to evaluate real-world effectiveness of NG when administered by the intended users (caregivers) in treating episodes of severe or moderate hypoglycaemia. The protocol defined severe hypoglycaemia as an episode wherein the patient was clinically incapacitated (that is, unconscious, convulsions, severe mental disorientation) to the point where the patient required third-party assistance to treat the hypoglycaemia. Moderate hypoglycaemia was defined as an episode wherein the person with diabetes showed signs of neuroglycopenia, with a glucometer reading of approximately 60 mg/dL (3.3 mmol/L) or less based on a blood sample taken at or near the time of treatment. Patients who had a history of severe episodes of hypoglycaemia were not excluded from the study. The study participants were asked to use 1 dose of NG 3 mg per event, as necessary, for up to 6 months to treat incident episodes of severe or moderate hypoglycaemia.

Because some patients had multiple events in Study B002, number of events rather than number of patients is presented. A total of 157 hypoglycaemic events (from 69 patients) were evaluable, of which 151 (96.2%) met the primary endpoint, defined as patients awakened or returned to normal status within 30 minutes following NG administration. The 6 events (3.8%) not resolved within 30 minutes were all moderate hypoglycaemic events; 1 had a blood glucose level that returned to normal (>70 mg/dL [3.9 mmol/L]) by 30 minutes but had a persistent headache, and 5 events had returned to normal status between 30 and 45 minutes without the use of additional measures to raise glucose levels. Importantly, all severe hypoglycaemic events (n=12) resolved, and patients regained consciousness, stopped convulsions, or returned to normal status (for those who were conscious before treatment) within 15 minutes of NG administration. Patients who experienced multiple severe hypoglycaemic events

responded successfully with each NG treatment. In this study, no caregivers called for external professional emergency medical assistance. In addition, most of the hypoglycaemic events, caregivers reported that it was easy to administer NG (80.5% of events) and that they were satisfied with the use of NG (94.4% of events).

2.4.2. Discussion on clinical efficacy

One additional study was conducted in the new targeted indication (children aged 1 to 4 years): Study IGBO. This study was small (n=7) and there was no control arm.

In the previously assessed Study IGBC, in response to insulin-induced hypoglycaemia, which was a surrogate to evaluate efficacy, NG produced clinically meaningful benefit to adult patients with T1D or T2D by restoring plasma glucose to normal levels (≥70 mg/dL [3.9 mmol/L]) or by increasing ≥20 mg/dL (1.1 mmol/L) from glucose nadir within 30 minutes in 98.7% of patients, and demonstrated non-inferiority to IMG. These finding were confirmed with clinical bridging and confirmatory Study IGBI.

In the previously assessed paediatric Study IGBB, 100% of patients 4 to <18 years old with T1D achieved an increase in glucose of ≥25 mg/dL (1.4 mmol/L) within 20 minutes of NG administration.

Similarly, in the paediatric Study IGBO, currently submitted for assessment, 100% of patients 1 to <4 years old with T1D achieved an increase in glucose of ≥20 mg/dL (1.1 mmol/L) increases within 30 minutes post dose.

The Applicant has proposed 3 mg as the registered dose for the treatment of hypoglycaemia in this age group, aligning with the dosage for older children (>4 years) and adults. In IGBO trial, nasal glucagon 3 mg was well tolerated in patients aged 1 to <4 years and resulted in blood glucose increases of >20 mg/dL (1.11 mmol/L) from nadir levels, which were within the normoglycaemic range, within 10–30 minutes post-dose in this population.

At the same time, the Applicant attributed the potentially lower bioavailability observed in study IGBO to the smaller nasal mucosal surface area in very young children. To ensure that the dose is optimally chosen with appropriate bioavailability in this age group, intranasal medication delivery required further discussion. The extent of drug absorption through the nasal route — ultimately determining systemic exposure and effect — was unclear in children aged 1-4 years. The Applicant was therefore requested to comment on potential absorption differences due to factors such as smaller nasal anatomy, underdeveloped sinuses, and specific mucosal characteristics. The Applicant has adequately responded to these concerns.

It should be noted that, since inducing hypoglycaemia in the paediatric population is considered unethical, efficacy was evaluated based on an increase in blood glucose of ≥20 mg/dL (1.1 mmol/L) and ≥25 mg/dL (1.4 mmol/L) from nadir, both within the normoglycaemic range, within 30 minutes of glucagon administration. Accordingly, in the paediatric trial involving participants aged 4–18 years, glucagon was administered after glucose was lowered to <80 mg/dL (4.44 mmol/L) using insulin on the dosing day. In the supportive paediatric trial (1-4 years), participants were recommended to fast overnight before the dosing visit on Day 1 to achieve a target blood glucose (BG) range of 70–140 mg/dL (3.9–7.8 mmol/L) at dosing.

In actual hypoglycaemia cases in the youngest group, the effect of the 3 mg NG dose of glucagon on blood glucose restoration may not be fully predictable based on the data from the paediatric trials. The physiological context, including glycogen stores in young children and the impact of recurrent hypoglycaemia, may differ from the study setting and could influence the glucagon response in real-

world hypoglycaemic events. This limitation of the development was noted, however was not considered critical.

Given the very high variability in glucagon concentrations observed in the limited dataset for patients aged 1 to <4 years from study IGBO, and the lack of a reliable paediatric popPK model due to previous GCP issues impacting study IGBB PK data, the absorption rate, bioavailability, and dosing consistency remain uncertain, making unpredictable the effect of systemic exposure across paediatric populations in hypoglycaemic conditions. However, given that the targeted PD results across all study populations showed similar outcomes at the proposed 3 mg dose, and this dose did not raise any safety concerns in the youngest children, its translation to real-world use in the treatment of hypoglycaemia is considered acceptable - especially since the induction of hypoglycaemia in paediatric clinical trials is limited because of ethical reasons.

2.4.3. Conclusions on the clinical efficacy

In conclusion, the overall results from the NG clinical development program have established that NG is efficacious for the intended indication.

2.5. Clinical safety

Patient exposure

The NG clinical development program is comprised of nine (9) completed studies in adults with or without diabetes mellitus and three (3) completed studies in children and adolescents with diabetes mellitus (see Table 7), for a total of 506 healthy subjects and patients who received the study drug.

Specifically, 468 participants received at least 1 dose of NG (including 428 participants who received NG 3 mg), and 234 participants received at least 1 dose of injectable glucagon.

The majority of the patients with diabetes enrolled in the NG clinical development program were adults with T1D. Forty-four (44) adults with T2D received at least 1 dose of NG, and 20 received injectable glucagon.

A total of 77 paediatric patients with T1D (1 to <18 years of age) participated in clinical studies: 65 patients received at least 1 dose of NG, and 24 patients received at least 1 dose of weight-based IMG.

Adverse events

In adult pivotal Study IGBC, paediatric pivotal Study IGBB, and adult clinical bridging and confirmatory Study IGBI, at least 1 treatment-emergent adverse event (TEAE) was reported by 55.4%, 55.6%, and 48.6%, respectively, of patients treated with NG, and by 45.1%, 75.0%, and 50.7%, respectively, of patients treated with IMG.

The very commonly reported (≥10%) TEAEs for patients of these 3 studies treated with NG 3 mg are shown in Table 11. For all 3 studies, these TEAEs were nausea, vomiting, and headache. The clinical concept of "upper respiratory tract irritation" was also very common in the 2 pivotal studies. "Upper respiratory tract irritation" is a cluster term for the nasal/respiratory/anosmia subset of TEAEs combined, and includes Preferred Terms (PTs) such as Rhinorrhea, Nasal congestion, Nasal discomfort, and Sneezing.

The very commonly reported TEAEs for patients treated with IMG included nausea and vomiting in all 3 studies as well as headache in Studies IGBB and IGBI, which are also shown in the table.

Table 11. Very Commonly Reported (≥10%) TEAEs by Preferred Term for the Two Pivotal Studies (IGBC, IGBB) and the Clinical Bridging and Confirmatory Study (IGBI)

Preferred Term	Adult Pivotal Study IGBC n (%)		Pediatric Pivotal Study IGBB n (%)		Clinical Bridging & Confirmatory Study IGBI n (%)	
	IMG 1 mg (N=82)	NG 3 mg (N=83)	IMG[a] (N=24)	NG 3 mg (N=36)	IMG 1 mg (N=69)	NG 3 mg (N=70)
Patients reporting ≥1 TEAE	37 (45.1)	46 (55.4)	18 (75.0)	20 (55.6)	35 (50.7)	34 (48.6)
Nausea	22 (26.8)	18 (21.7)	8 (33.3)	6 (16.7)	29 (42.0)	22 (31.4)
Vomiting	9 (11.0)	13 (15.7)	9 (37.5)	11 (30.6)	12 (17.4)	10 (14.3)
Headache	7 (8.5)	17 (20.5)	3 (12.5)	9 (25.0)	7 (10.1)	11 (15.7)
"Upper Respiratory Tract Irritation"	1 (1.2)	16 (19.3)	0 (0)	6 (16.7)	1 (1.4)	3 (4.3)

Abbreviations: IMG = intramuscular glucagon; N = total number of patients; n = number of patients in the specified category; NG = nasal glucagon; TEAE = treatment-emergent adverse event.

[a] Weight-based dosing of IMG (0.5 mg or 1 mg) was used in the pivotal pediatric trial.

Source: CLUWE: //statsclstr//lillyce/prd/ly900018/i8r_mc_igbc/final/output/shared/tfl/igbc_smtea111.rtf; //statsclstr//lillyce/prd/ly900018/idb/output/shared/smtea112.rtf; //lillyce/prd/ly900018/i8r_mc_igbi/csr1/output/shared/t_aef1.

Nausea and Vomiting

Nausea and vomiting have been reported for the currently marketed injectable glucagon products (Glucagon for Injection Product Monograph, 2012; GlucaGen HypoKit UK SmPC, 2015; GlucaGen HypoKit USPI, 2015; GlucaGen HypoKit Product Monograph, 2016; Glucagon for Injection USPI, 2017). These events were very commonly reported at similar frequencies across studies for adult and paediatric patients administered NG 3 mg or IMG. These events were typically mild or moderate in severity, and none were serious.

These data do not indicate an increased occurrence of nausea and vomiting with NG treatment beyond the currently marketed injectable glucagon therapies.

Immunogenicity and Hypersensitivity Reactions

Consistent with the immunogenic properties of protein and peptide therapeutics, individuals exposed to NG could develop an immune response, including formation of antidrug antibodies (ADA). Data from 3 studies of the NG development program (Studies IGBF, IGBG, and B002) demonstrated minimal incidence (2%) of treatment-emergent antidrug antibodies (TE ADA) for NG. None of the patients with TE ADA experienced a hypersensitivity AE, and no patient developed neutralizing antibodies. These results suggest there is a very low probability of immunogenic reaction following NG administration.

Hypersensitivity reactions, including anaphylaxis, have been reported for the currently marketed injectable glucagon products (Glucagon for Injection Product Monograph, 2012; GlucaGen HypoKit UK SmPC, 2015; GlucaGen HypoKit USPI, 2015; GlucaGen HypoKit Product Monograph, 2016; Glucagon for Injection USPI, 2017). The occurrence of events that could be related to hypersensitivity was low and

occurred only in adult patients (NG, 4.3% [n=10]; injectable glucagon, 1.4% [n=2]). The most predominantly reported event was pruritus, which occurred in 0% to 3.6% of patients in Studies IGBI and IGBC. Reported hypersensitivity events were typically mild or moderate in severity, and none were serious. No patients discontinued due to a hypersensitivity event.

These data do not indicate an increased risk of systemic hypersensitivity events with NG treatment beyond the currently marketed injectable glucagon therapies.

Increases in Blood Pressure and Heart Rate

Transient increases in blood pressure and heart rate have been reported for the currently marketed injectable glucagon products (Glucagon for Injection Product Monograph, 2012; GlucaGen HypoKit UK SmPC, 2015; GlucaGen HypoKit USPI, 2015; GlucaGen HypoKit Product Monograph, 2016; Glucagon for Injection USPI, 2017). In the adult and paediatric pivotal Studies IGBC and IGBB, and the clinical bridging and confirmatory Study IGBI, vital signs were assessed at baseline and at 45 minutes post glucagon administration. From these data, shift analyses were performed to identify individuals with increases in blood pressure and heart rate beyond the standard reference ranges. More NG-treated patients shifted beyond the reference range values than IMG-treated patients but the incidence in both groups was small, and none of the values were considered clinically significant by the investigators or the Sponsor. These assessments were consistent in both adult and paediatric patients and were supported by all available data of the NG clinical development program.

In addition, mean change analyses were performed. Small mean changes in systolic blood pressure, diastolic blood pressure, and heart rate were observed for adult patients treated with NG 3 mg or IMG 1 mg, as shown in Table 12.

Table 12. Mean Changes in Vital Signs of Adult Patients, from Baseline to 45 Minutes Following Glucagon Administration

	Study IGBC		Study IGBI	
Parameter	**IMG 1 mg**	**NG 3 mg**	**IMG 1 mg**	**NG 3 mg**
Time Point	**(N=81)**	**(N=82)**	**(N=69)**	**(N=70)**
SBP (mm Hg)	–6.4	0.8	–3.0	3.7
DBP (mm Hg)	–6.5	–0.6	–2.2	3.0
Pulse (bpm)	–5.0	–3.4	–1.9	–1.9

Abbreviations: DBP = diastolic blood pressure; IMG = intramuscular glucagon; N = total number of patients; NG = nasal glucagon; SBP = systolic blood pressure.

Sources: IGBC CSR, Table 14.4-18; IGBI, CLUWE: //lillyce/prd/ly900018/i8r_mc_igbi/csr1/output/shared/t_vs

No consistent findings for the mean changes in vital signs were observed among the 3 paediatric age groups assessed in Study IGBB.

There were no clinically significant findings in vital signs measurements or other observations related to safety during the study IGBO (See IGBO CSR).

Table 2. IGBO Summary of Adverse Events

	Number of events (number of participants with events) [percentage of participants with events]
	3 mg nasal glucagon (N = 7)
All TEAEs	9 (5) [71.4%]
Mild	9 (5) [71.4%]
Moderate	0
Severe	0
Treatment-related TEAEs	9 (5) [71.4%]
Fatal AEs	0
SAEs	0
AEs leading to discontinuation of study intervention	0
Nasal, respiratory, and anosmia AEs	3 (2) [28.6%]

Abbreviations: AE = adverse event; N = number of participants studied; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Study IGBO Incidence of TEAEs

During the study, a total of 9 TEAEs were reported by 5 of the 7 participants, each considered to be related to NG by the investigator. The TEAEs reported by the 5 participants comprised:

- Dyspepsia reported by 1 participant on Day 1, approximately 2 hours post-dose, that resolved after 15 minutes.
- Eye pruritus reported in 1 participant on Day 1, 15 minutes post-dose, that resolved after 31 minutes. One event of post-tussive vomiting was reported on Day 2, approximately 36 hours post-dose for the same participant.
- Epistaxis was reported in 1 participant at 1-minute post-dose, followed by sneezing at 7 minutes post-dose. Both events resolved within 1 minute of onset.
- Nasal discomfort was reported by 1 participant at 1-minute post-dose that resolved after approximately 4 hours. Vomiting and Abdominal discomfort were also reported on Day 1, approximately 1.5 hours post-dose by the same participant. Both events had resolved within 3 hours of onset.
- Nausea was reported by 1 participant on Day 1, approximately 2 hours post-dose, that resolved approximately 20 hours after onset.

From the literature, increases in mean heart rate and blood pressure after glucagon administration have been reported. The mean increases in systolic blood pressures were 8 to 16 mmHg, diastolic blood pressures were 3 to 6 mmHg, and heart rate were 9 to 11 bpm. While these effects have been reported as transient, vital sign assessments beyond 30 minutes have not been systematically studied. Because of the differences in the timing of the assessments in the NG program (45 minutes) versus the historical data (≤30 minutes), no direct comparisons can be made.

While small differences in vital sign changes were observed for NG relative to IMG, the magnitude of these changes is not considered clinically significant. Therefore, these data do not indicate the occurrence of clinically meaningful increases in blood pressure and heart rate with NG treatment beyond the currently marketed injectable glucagon products.

Upper Respiratory Tract Irritation Events

"Upper respiratory tract irritation" events were very commonly reported for patients treated with NG 3 mg and were not generally reported by patients treated with injectable glucagon. These events were typically mild or moderate in severity and resolved within 1 day; none were serious.

In addition to spontaneously reported AEs, severity and duration of symptoms related to nasal administration were assessed with the Nasal and Non-Nasal Score Questionnaire as part of the controlled studies. The severity of these symptoms peaked at 15 minutes and then declined to near-baseline levels by the last time point assessed (1.5 to 4 hours post-dose) for adult and paediatric patients.

These assessments were supported by all available data of the NG clinical development program.

Headache

Headache events were commonly reported in patients treated with NG 3 mg or IMG 1 mg but were reported more frequently for patients treated with NG. These events were typically mild or moderate in severity and resolved within 1 day; none were serious.

These assessments were supported by all available data of the NG clinical development program.

Serious adverse event/deaths

Across all 12 completed studies of the NG clinical development program, 1 death (adult treated with NG) and 2 serious adverse events (SAEs) (1 adult treated with NG, 1 paediatric patient treated with IMG) were reported.

None of these events were considered to be related to study treatment by either the study investigators or the Sponsor; however, the SAE of severe hypoglycaemia in the paediatric patient with T1D treated with IMG was considered related to study procedures.

Safety in special populations

Intrinsic Factors

The TEAEs of the NG clinical development program were compared across subgroups based on intrinsic factors, including gender, age, and race, to evaluate possible group differences in response to NG. There were no differences found for gender or diabetes type (T1D or T2D), and too few participants were enrolled to draw meaningful conclusions about elderly patients or races other than white. In support, there are no known safety differences across these factors for the currently marketed injectable glucagon products (Glucagon for Injection Product Monograph, 2012; GlucaGen HypoKit UK SmPC, 2015; GlucaGen HypoKit USPI, 2015; GlucaGen HypoKit Product Monograph, 2016; Glucagon for Injection USPI, 2017).

Extrinsic Factors

Other studies of the NG clinical development program were conducted to evaluate extrinsic factors that may impact the safety or pharmacologic response to NG, including the effects of the common cold and concomitant administration of nasal decongestant (oxymetazoline). Overall tolerance of NG was similar in patients with or without symptoms of a common cold and in patients with or without coadministration of a decongestant. These findings indicate that NG may be used for the treatment of severe hypoglycaemia in patients with symptoms of the common cold or taking decongestants.

Post marketing experience

In the EU, NG has been marketed for severe hypoglycaemia since 2019. As of July 2024, NG has been authorized in 40 countries, including those in the EU, Canada, Japan, and Switzerland.

Cumulatively as of July 24, 2024, it is estimated that approximately 1,029,003 patients have been exposed to NG worldwide in the post-marketing setting.

The AE profile has continued to be generally consistent across clinical trials for severe hypoglycaemia indication at 3 mg as well as in the post-marketing database.

Upon review of the reported reactions up to July 2024, no new safety information was identified:

- No new signals were identified during this reporting period.
- Following the review of serious hypersensitivity events (considered as a key risk for NG), there was no new information or data relevant to this risk that would warrant reclassifying it as an important potential risk.
- No significant actions related to safety, such as suspension, withdrawal, or temporary halt or premature ending of clinical trial for safety reasons were reported.
- No patterns of NG use including overdose, abuse, misuse, and use beyond the recommendation in the reference product information were observed.

Considering post-marketing data, the safety profile for NG in severe hypoglycaemia remains unchanged.

The most commonly reported adverse reactions in patients treated with NG for the treatment of severe hypoglycaemia at 3 mg were lacrimation increased (36%), upper respiratory tract irritation (34%), nausea (27%), headache (21%), and vomiting (16%). These adverse reactions were all of mild or moderate severity.

2.5.1. Discussion on clinical safety

The safety profile of NG includes well-known effects of glucagon treatment as well as local tolerability effects that have been observed with other medications delivered via the nasal route. These adverse effects are transient and are non-serious in nature. As such, no important identified risks have been observed in the NG program.

Inappropriate use of the device leading to loss of drug benefit is considered an important potential risk, for which minimisation is addressed through educational materials proposed to provide guidance.

Regarding intranasal medication delivery issues, the Applicant assumes that the volume of the NG 3 mg powder (0.09 mL) should be acceptable for nasal administration in small children within this age group (aged 1 to <4 years). At the same time, the Applicant attributes the potentially lower bioavailability observed in study IGBO to the smaller nasal mucosal surface area in these very young children.

However, in children aged 1-4 years, the extent of drug absorption through the nasal route — ultimately determining systemic exposure and effect — remained unclear. The Applicant was therefore requested to comment on potential absorption differences due to factors such as smaller nasal anatomy, underdeveloped sinuses, and specific mucosal characteristics. The Applicant has adequately responded to these concerns. The acceptability of the volume of NG 3 mg powder (0.09 mL) for the nasal administration in young children is supported by the absence of difference in efficacy, irrespectively of any potential differences in nasal anatomy or mucosal characteristics.

In this context, the suitability of the proposed device for administration in this youngest population is particularly relevant. The Applicant has explained that the diameter of the device tip is small enough to safely enter the nostril opening. However, it was not clear during assessment whether the tip length is appropriate and whether the dispersion pressure of the powder is suitable for effective delivery in small nasal cavities, given that the volume of the youngest children's Nasal Volume is not well documented in the literature.

The Applicant was requested to provide a detailed description of the device and confirm its suitability for use in this population, along with a discussion on the appropriateness of the fixed dosing approach. The Applicant has adequately responded to these concerns. Only the tip insertion is sufficient which is reassuring. Although 3 mg NG in 1 to <4-year-old participants initially was expected to result in higher systemic glucagon concentrations than those observed with 3 mg NG in older paediatric patients, this transient high systemic exposure is expected to be safe, especially because this is a one-time administration.

Generalized allergic reactions have been reported, as for the currently approved injectable glucagon products. This is a considered to be a potential risk for NG and is mentioned in the labelling.

The safety database for NG is considered sufficient in size and scope to adequately characterize the safety profile of NG in adult and paediatric patients with diabetes given the intended use of NG and the history of safe use with the currently approved injectable glucagon products.

The adverse effects and the potential risk associated with NG will continue to be managed through routine measures including labelling and pharmacovigilance activities.

2.5.2. Conclusions on clinical safety

The clinical safety of NG in the new proposed population (paediatric patients aged 1 to 4 years old) is sufficiently demonstrated.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version 1.1 with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 1.1 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 1.1 with the following content:

Safety concerns

Table 14. Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Inappropriate use of the device leading to loss of drug benefit
Missing information	None

Pharmacovigilance plan

No changes were proposed to the Pharmacovigilance plan. Minor editorial amendments were made, which are considered acceptable.

Risk minimisation measures

No changes were proposed to the routine or additional risk minimisation measures.

Currently, additional risk minimisation measures are in the form of 1) a demonstration kit that includes a trainer device with an administration leaflet unique to the trainer device, 2) an administration leaflet and 3) an online instructional video are in place to address the important potential risk of "*Inappropriate use of the device leading to loss of drug benefit*".

No changes to the device have been presented for the proposed population, aged 1 to <4 years. Within this procedure, the MAH provided a justification that the current device will be compatible for the use in the younger population (1-<4 years of age). The justification is considered acceptable, therefore no amendments or new aRMMs are proposed. However, the MAH is reminded to ensure that the content of the aRMMs is aligned with the indications, in particular ensuring that the new age group is appropriately reflected in the materials.

Minor editorial amendments were also made, which are considered acceptable.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet (PL) has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: due to the very limited number of updates introduced to the Package leaflet by the present variation, neither content nor layout are impacted. Therefore, a new user testing or bridging study is not deemed necessary.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Severe hypoglycaemia is defined as an episode of hypoglycaemia that requires the assistance from another person to actively administer carbohydrates, glucagon, or take other corrective actions. Severe hypoglycaemia affects approximately 30% (range, 22% to 46%) of patients with T1D annually, at a frequency of 30 to 320 events per 100 patient-years. In insulin-treated patients with T2D, severe hypoglycaemia affects 7% to 25%, at a frequency of 10 to 80 events per 100 patient-years.

Severe hypoglycaemia has serious clinical implications for patients with T1D or T2D and can be life threatening. It has been associated with cognitive impairment, behavioural changes, seizures, coma, death; falls, fractures, motor vehicle accidents; arrhythmias, decreased quality of life; onset or acceleration of dementia or cognitive decline; impaired hypoglycaemic awareness; and prevention of optimal glycaemic control. Because diabetic patients are at risk for severe hypoglycaemia, due to the nature of the disease condition and management, treatment goals for managing severe hypoglycaemia are to return, as soon as possible after event onset, the patient's blood glucose to normal levels or recover sufficiently enough to restore cognitive function so that the patient may safely consume oral carbohydrates in order to minimize damage.

Injectable glucagon products have been used clinically to treat severe hypoglycaemia for more than 50 years, and the benefits and risks associated with these products are well established.

Patient education and frequent blood glucose monitoring can minimise the risk for severe hypoglycaemia; however, even compliant and motivated patients remain at risk for this serious complication of diabetes therapy. Thus, as with all potentially life-threatening clinical conditions, patients at risk for severe hypoglycaemia and their caregivers should always have rescue therapy options available.

3.1.2. Available therapies and unmet medical need

Currently available treatments for severe hypoglycaemia are limited to intravenous dextrose and injectable glucagon; however, intravenous dextrose requires administration by trained personnel within a hospital or emergency medical setting. The treatment of severe hypoglycaemia outside of these settings is mainly limited to injectable glucagon, but injectable glucagon is currently not available in a ready-to-use formulation.

Glucagon is not stable in the aqueous state; therefore, the currently available glucagon powder in glucagon emergency kits must be reconstituted using a multiple-step process before the drug can be administered to the patient by either subcutaneous or intramuscular injection. Because the patient is either semi-conscious or comatose and thus unable to prepare an injection of glucagon for self-administration during an event, someone else (friend, teacher, coworker, spouse, parent) must be able to correctly prepare and administer the dose. Errors in using the existing glucagon kits may occur for various reasons, such as needle damage, dropped materials, secondary needle stick, injecting diluent alone, or miscalculation of dose for paediatric patients (weight-based dosing), especially if the caregiver becomes stressed or panics during the emergency situation, which may also be coupled with fear of giving injections. This multistep process coupled with administration errors may delay or even preclude treatment, especially in emergencies when the caregivers do not have medical training and are either unfamiliar with needles and syringes or have a general fear of needles.

All of these challenges not only result in underutilization of an efficacious treatment for severe hypoglycaemia but also have left patients and their caregivers asking for a better solution, possibly for decades. In 1997, Yanai and colleagues published an article indicating that the majority of patients surveyed (82%) believed that their caregivers would prefer to administer glucagon nasally, as opposed to intramuscular or subcutaneous injection. Twenty years later, there is some evidence that caregivers may still want other treatment options. An easy-to-use, alternative method of glucagon delivery may provide a better option for some caregivers for the management of an important complication of diabetes - severe hypoglycaemia.

3.1.3. Main clinical studies

3.2. Favourable effects

Results from the NG clinical development program have established that NG is efficacious for the intended indication. In response to insulin-induced hypoglycaemia, which was a surrogate to evaluate efficacy, NG produced clinically meaningful benefit to adult patients with T1D or T2D (Study IGBC) by restoring plasma glucose to normal levels (≥70 mg/dL [3.9 mmol/L]) or by increasing ≥20 mg/dL (1.1 mmol/L) from glucose nadir within 30 minutes in 98.7% of patients, and demonstrated non-inferiority to IMG. These finding were confirmed with clinical bridging and confirmatory Study IGBI. In the pivotal paediatric study (Study IGBB), 100% of patients 4 to <18 years old with T1D achieved an increase in glucose of ≥25 mg/dL (1.4 mmol/L) within 20 minutes of NG administration. Similarly, in the supportive paediatric study (Study IGBO), assessed within current procedure, 100% of patients 1 to <4 years old with T1D achieved an increase in glucose of ≥20 mg/dL (1.1 mmol/L) increases within 30 minutes post dose.

3.3. Uncertainties and limitations about favourable effects

The patient populations of the NG clinical studies were generally homogenous and largely composed of white, non-elderly adult (<65 years) and paediatric patients from the US, Canada, and Germany. However, the lack of diversity in patients included in the NG clinical development program is mitigated by the well-established mechanism of action of glucagon and decades of its clinical use as a treatment for severe hypoglycaemia. Other reported clinical experience has not identified differences in glucagon responses between the elderly and younger patients (Glucagon for Injection Product Monograph, 2012; GlucaGen HypoKit UK SmPC, 2015; GlucaGen HypoKit USPI, 2015; GlucaGen HypoKit Product Monograph, 2016; Glucagon for Injection USPI, 2017).

One additional study was conducted in the new targeted indication (children aged 1 to 4 years): Study IGBO. This study was small (n=7) and there was no control arm. Therefore, some uncertainty remains about the efficacy in these very young patients. This limitation is acknowledged however not considered a blocking issue.

It should be noted that, since inducing hypoglycaemia in the paediatric population is considered unethical, efficacy was evaluated based on an increase in blood glucose of ≥20 mg/dL (1.1 mmol/L) and ≥25 mg/dL (1.4 mmol/L) from nadir, both within the normoglycaemic range, within 30 minutes of glucagon administration. Accordingly, in the pivotal paediatric trial involving participants aged 4–18 years, glucagon was administered after glucose was lowered to <80 mg/dL (4.44 mmol/L) using insulin on the dosing day. In the supportive paediatric trial, Study IGBO (in patients 1–4 years old), participants

were recommended to fast overnight before the dosing visit on Day 1 to achieve a target blood glucose (BG) range of 70–140 mg/dL (3.9–7.8 mmol/L) at dosing.

In actual hypoglycaemia cases in the youngest group, the effect of the 3 mg NG dose of glucagon on blood glucose restoration may not be fully predictable based on the data from the paediatric trials. The physiological context, including glycogen stores in young children and the impact of recurrent hypoglycaemia, may differ from the study setting and could influence the glucagon response in real-world hypoglycaemic events. This uncertainty is however not considered to be a blocking issue.

Given the very high variability in glucagon concentrations observed in this limited dataset for patients aged 1 to <4 years from study IGBO, and the lack of a reliable paediatric popPK model due to GCP issues with study IGBB, the absorption rate, bioavailability, and dosing consistency remain unclear, making the effect of systemic exposure across paediatric populations in hypoglycaemic conditions unpredictable. However, given that the PD results across all study populations showed similar outcomes at the proposed 3 mg dose, and this dose did not raise any safety concerns in the youngest children, its translation to real-world use in the treatment of hypoglycaemia is considered acceptable - especially since the induction of hypoglycaemia in paediatric clinical trials is limited because of ethical reasons.

3.4. Unfavourable effects

The safety profile of NG includes well-known effects of glucagon treatment as well as local tolerability effects that have been observed with other medications delivered via the nasal route. These adverse effects are transient and are non-serious in nature. As such, no important identified risks have been observed in the NG development program.

Inappropriate use of the device leading to loss of drug benefit is considered an important potential risk, for which minimisation is addressed through agreed educational materials.

Generalized allergic reactions have been reported, as observed with the currently approved injectable glucagon products. This is considered to be a probable risk for NG and is mentioned in the labelling.

The safety database for NG is considered sufficient in size and scope to adequately characterize the safety profile of NG in adult and paediatric patients with diabetes given the intended use of NG and the history of safe use with the currently approved injectable glucagon products.

The adverse effects and the potential risk associated with NG will continue to be managed through routine measures including labelling and pharmacovigilance activities.

Overall, the safety data presented in this dossier demonstrate that NG is safe for the treatment of severe hypoglycaemia in adults, and paediatric patients aged 1 year and over with diabetes mellitus.

3.5. Uncertainties and limitations about unfavourable effects

One additional study was conducted in the new targeted indication (children aged 1 to 4 years): Study IGBO. This study was small (n=7) and there was no control arm. Therefore, some uncertainty remains about the safety in these very young patients. This is however not a blocking issue.

As with all development programs, the safety evaluation for NG could not detect very rare adverse effects, adverse effects with long latency, or adverse effects caused by prolonged or cumulative exposure. These limitations are less meaningful for NG because the treatment indication is for acute potentially life-saving episodic use, not chronic administration.

Regarding intranasal medication delivery issues, the Applicant assumes that the volume of the NG 3 mg powder (0.09 mL) should be acceptable for nasal administration in small children within this age group (aged 1 to <4 years). At the same time, the Applicant attributes the potentially lower bioavailability observed in study IGBO to the smaller nasal mucosal surface area in these very young children.

However, in children aged 1–4 years, the extent of drug absorption through the nasal route -ultimately determining systemic exposure and effect - remains unclear. The Applicant was therefore requested to comment on potential absorption differences due to factors such as smaller nasal anatomy, underdeveloped sinuses, and specific mucosal characteristics. The Applicant has adequately responded to these concerns

In this context, the suitability of the proposed device for administration in this youngest population is particularly relevant. The Applicant has explained that the diameter of the device tip is small enough to safely enter the nostril opening. However, it was unclear during the procedure whether the tip length is appropriate and whether the dispersion pressure of the powder is suitable for effective delivery in small nasal cavities, given that the nasal volume of the youngest children's is not well documented in the literature. The Applicant stated that only tip insertion is sufficient. This was reassuring however the Applicant was requested to provide a detailed description of the device and confirm its suitability for use in this population, along with a discussion on the appropriateness of the fixed dosing approach. The Applicant has adequately responded to these concerns.

3.6. Effects Table

Table 15. Effects Table for Nasal Glucagon indicated for the treatment of severe hypoglycaemia in adults, adolescents, and children aged 1 year and over with diabetes mellitus

Effect	Short Description	Unit	Treatment		Uncertainties/ Strength of evidence	References
			NG 3 mg	IMG a		
Favourable Effects						
Treatment Success	Adults: Proportion of patients with an increase in glucose to ≥70 mg/dL (3.9 mmol/L) or an increase of ≥20 mg/dL (1.1 mmol/L) from glucose nadir[b] within 30 minutes after receiving glucagon for insulin-induced hypoglycaemia, without receiving additional actions to increase the glucose level. Insulin infusion was stopped when glucose was <60 mg/dL (3.3 mmol/L).	%	98.7[(1)] 100[(2)]	100[(1)] 100[(2)]	Non-inferiority of NG to IMG was demonstrated in 2 active comparator-controlled adult studies. Hypoglycaemia with blood glucose <60 mg/dL (3.3 mmol/L) was used as a surrogate for severe hypoglycaemia.	(1) Adult Pivotal Study IGBC; (2) Adult Clinical Bridging and Confirmatory Study IGBI
Treatment Success	Paediatrics: Proportion of patients with an increase in glucose ≥20 mg/dL (1.1 mmol/L) from glucose nadir[b] within 30 minutes of glucagon administration, without receiving additional actions to increase the glucose level. Insulin was used if necessary to attain a glucose <80 mg/dL (4.4 mmol/L).		100	100	Consistent efficacy between the 2 treatments. Limited data on patients with blood glucose <70 mg/dL (3.9 mmol/L).	Paediatric Pivotal Study IGBB

Effect	Short Description	Unit	Treatment		Uncertainties/ Strength of evidence	References
			NG 3 mg	IMG a		
Effectiveness	Adults and Paediatrics: Proportion of moderate or severe hypoglycaemic events for which patients awakened or returned to a normal status within 30 minutes following NG administration.		96.2(1) 100(2)	N/A	Assessment based on caregiver's judgment. NG was administered by intended users (caregivers) in the real-world setting. No active comparator was included.	(1) Adult Actual-Use Study B002[d]; (2) Paediatric Actual-Use Study B001[e]
Usability	Proportion of caregivers who administered full doses of glucagon in a simulated use study after receiving training and instructions.	%	94	13	Although a simulated study, distracting sounds and other stressors were used to model the urgency and stress of a real-life severe hypoglycaemic event.	Simulation Study[f]
	Proportion of untrained acquaintances who administered full doses of glucagon in a simulated use study		93	0		
	Adults and Paediatrics: Proportion of hypoglycaemic events for which caregivers reported that NG was easy or very easy to administer.		80.5(1) 93.9(2)		An unvalidated questionnaire was used to evaluate the caregiver's assessment of the degree of difficulty using NG.	1)Adult Actual-Use Study B002[d]; (2) Paediatric Actual-Use Study B001[e]
	Adults and Paediatrics: Proportion of hypoglycaemic events for which caregivers were relatively satisfied, satisfied, or very satisfied with NG use		94.4(1) 93.9(2)		An unvalidated questionnaire was used to evaluate the caregiver's assessment of the degree of satisfaction using NG.	
Treatment success	Proportion of patients with an increase in glucose ≥20 mg/dL (1.1 mmol/L) from glucose nadir within 30 minutes of glucagon administration, without receiving additional actions to increase the glucose level.	%	100%	N/A.	Small open-label study (n=7) in children aged 1 to 4 years.	Study IGBO
Unfavourable Effects						
Nausea	Incidence	%	21.7(1) 31.4(2) 16.7(3)	26.8(1) 42.0(2) 33.3(3)	In general, these events were mild to moderate in severity and infrequently led to discontinuation. Rates of occurrence were similar between treatments.	(1) Adult Pivotal Study IGBC; (2) Adult Bridging and Confirmatory Study IGBI; (3) Paediatric Pivotal Study IGBB
Vomiting	Incidence		15.7(1) 14.3(2) 30.6(3)	11.0(1) 17.4(2) 37.5(3)		
Headache	Incidence		20.5(1) 15.7(2) 25.0(3)	8.5(1) 10.1(2) 12.5(3)	In general, these events were mild to moderate in severity and infrequently led to discontinuation.	
URTI[c]	Incidence		19.3(1) 4.3(2) 16.7(3)	1.2(1) 1.4(2) 0(3)		

Effect	Short Description	Unit	Treatment		Uncertainties/ Strength of evidence	References
			NG 3 mg	IMG a		
Pruritus	Incidence		3.6(1) 0(2) 0(3)	1.2(1) 0(2) 0(3)	No anaphylaxis or serious hypersensitivity AEs were reported. There were no discontinuations for the related event of pruritus.	

Abbreviations: AEs = adverse events; NG = nasal glucagon; IMG = intramuscular glucagon; N/A = not applicable; URTI = upper respiratory tract irritation.

a *Dosing of IMG 0.5 mg or 1 mg (based on body weight) was used in the pivotal paediatric trial, and IMG 1 mg was used for adults. Dosing with IMG followed current labeling for the marketed products.*

b *Nadir was defined as the minimum glucose value at the time of or within 10 minutes following glucagon administration.*

c *URTI includes rhinorrhea, nasal discomfort, nasal congestion, and sneezing.*

d *Seaquist ER, et al. Prospective study evaluating the use of nasal glucagon for the treatment of moderate to severe hypoglycaemia in adults with type 1 diabetes in a real-world setting. Diabetes Obes Metab. 2018;20(5):1316-1320.*

e *Deeb LC, et al. A phase 3 multicenter, open-label, prospective study designed to evaluate the effectiveness and ease of use of nasal glucagon in the treatment of moderate and severe hypoglycaemia in children and adolescents with type 1 diabetes in the home or school setting. Pediatr Diabetes. 2018; In press.*

f *Yale JF, et al. Faster use and fewer failures with needle-free nasal glucagon versus injectable glucagon in severe hypoglycaemia rescue: a simulation study. Diab Technol Ther. 2017;19(7):423-432.*

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Severe hypoglycaemia is one of the most serious acute complications of diabetes treatment. In the supportive paediatric study (Study IGBO), 100% of patients 1 to <4 years old with T1D achieved an increase in glucose of ≥20 mg/dL (1.1 mmol/L) within 30 minutes post dose.

The safety profile of NG includes well-known effects of glucagon treatment as well as local tolerability effects that have been observed with other medications delivered via the nasal route.

3.7.2. Balance of benefits and risks

The benefit-risk balance for NG is well established in older children and adults. The administration of glucagon in very young children (1–4 years) is also clinically well-established, albeit traditionally via injectable routes. The question, therefore, lies in the appropriateness of the nasal formulation for this specific age group. The Applicant has adequately responded to this concern.

NG addresses an unmet medical need of diabetic patients and their caregivers and contributes to improved patient care also in patients aged 1 to 4 years.

Extrapolation of data from older patients to patients aged 1 to 4 years is possible to a certain degree.

There is one additional study (IGBO) in patients aged 1 to 4 years. However, this was a small (n=7) open label study. The safety profile of NG in this study was similar to the one in the previous trials. All participants achieved treatment success within the 30-minutes post dose assessment window. In individual participants, the actual time to treatment success ranged from 10 to 30 minutes, with a

mean time to success of 15.6 minutes. Due to ethical constraints, clinical trials in this age group cannot rely on induced hypoglycaemia or placebo-controlled designs. This only available study, which was open label, conducted in normoglycaemic children, demonstrated a sustained increase in glucose levels following administration; however, the effect of NG in actual hypoglycaemic episodes may differ from these controlled conditions. This is however not a blocking issue.

Thus, extrapolation based on a PK bridge from older children/adults is not possible and the pivotal data will be the efficacy and safety results for the 7 children included in the IGBO study. This is a small data set, but sufficient considering the well-known mechanism of action.

Results from the NG clinical development program have established that NG is efficacious for the intended indication, but some non-blocking uncertainties remain (see above).

The Applicant has provided more information on the device and the method of administration. The fact that tip insertion is sufficient is reassuring.

From a safety perspective, the adverse event profile in very young children does not appear to differ significantly from that observed in older children and adults.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Baqsimi in the treatment of severe hypoglycaemia in adults, adolescents, and children aged 1 year and over with diabetes mellitus is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	Addition of a new therapeutic indication or modification of an approved one.	Type II	I and IIIB

Extension of indication to include treatment of severe hypoglycaemia in paediatric patients aged 1 and over with diabetes mellitus for BAQSIMI based on final results from study I8R-MC-IGBO; this is an Open-Label, Multi-Center, Single-Dose Study to Assess the Safety, Tolerability, Pharmacodynamics, and Pharmacokinetics of Nasal Glucagon in Paediatric Patients with Type 1 Diabetes Aged 1 to <4 years; as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 1.1 of the RMP has also been submitted. In addition, the

Marketing authorisation holder (MAH) took the opportunity to introduce a correction in the Package Leaflet.

The variation leads to amendments to the annexes I and IIIB and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I and IIIB and to the Risk Management Plan are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0301/2020 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the "EPAR- Procedural steps taken and scientific information after authorisation" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion "EMA/VR/0000244909"

Attachments

1. SmPC and Package Leaflet (changes highlighted) as adopted by the CHMP on 24 July 2025.

Reminders to the MAH

1. In accordance with Article 13(3) of Regulation (EC) No 726/2004 the Agency makes available a European Public Assessment Report (EPAR) on the medicinal product assessed by the Committee for Medicinal Products for Human Use. The EPAR is first published after the granting of the initial marketing authorisation (MA) and is continuously updated during the lifecycle of the medicinal product. In particular, following a major change to the MA, the Agency further publishes the assessment report of the CHMP and the reasons for its opinion in favour of granting the change to the authorisation, after deletion of any information of a commercially confidential nature.

   Should you consider that the CHMP assessment report contains commercially confidential information, **please provide the EMA Procedure Assistant your proposal for deletion of commercially confidential information** (CCI) in "track changes" and with detailed justification by 10 August 2025 The principles to be applied for the deletion of CCI are published on the EMA website at https://www.ema.europa.eu/en/documents/other/heads-medicines-agencies/european-medicines-agency-guidance-document-identification-commercially-confidential-information_en.pdf

   In addition, should you consider that the CHMP assessment report contains personal data, please provide the EMA Procedure Assistant your proposal for deletion of these data in "track changes" and with detailed justification by 10 August 2025. We would like to remind you that, according to Article 4(1) of Regulation (EU) 2016/679 (General Data Protection Regulation, "GDPR") 'personal data' means any information, relating to an identified or identifiable natural person (the 'data subject'). An identifiable natural person is one who can be identified, directly or indirectly, in particular by reference to an identifier such as a name, an identification number, location data, an online identifier or to one or more factors specific to the physical, physiological, genetic, mental, economic, cultural or social identity of that natural person.

   It is important to clarify that pseudonymised data are also considered personal data. According to Article 4(5) of GDPR pseudonymisation means that personal data is processed in a manner that the personal data can no longer be attributed to a specific data subject without the use of additional information (e.g. key-coded data).

   Accordingly, the name and the patient identification number are two examples of personal data which may relate to an identified or identifiable natural person. The definitions also encompass for instance: office e-mail address or phone number of a company, data concerning health, e.g. information in medical records, clinical reports or case narratives which relates to an identifiable individual."

2. The MAH is reminded to submit an eCTD closing sequence with the final documents provided by Eudralink during the procedure (including final PI translations, if applicable) within 15 days after the Commission Decision, if there will be one within 2 months from adoption of the CHMP Opinion, or prior to the next regulatory activity, whichever is first. If the Commission Decision will be adopted within 12 months from CHMP Opinion, the closing sequence should be submitted within 30 days after the Opinion. For additional guidance see chapter 4.1 of the Harmonised Technical Guidance for eCTD Submissions in the EU.

3. If a revised RMP is being approved as part of this procedure, **please send to the EMA Procedure Assistant** one redacted PDF document containing the RMP body, Annex 4 and Annex 6, as applicable, together with a redacted RMP file that can show the content that is proposed for redaction, and the signed RMP Publication Declaration, **by** 10 August 2025.